

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-786

MEDICAL REVIEW

Division Director and Acting Office Director Review

**NDA 50-786
Pylera[™] Capsules
(biscalcitrates/metronidazole/tetracycline hydrochloride)**

NDA: 50-786

Drug: Pylera[™] Capsules (formerly Helizide[®] and Helicide)
(biscalcitrates, metronidazole, and tetracycline hydrochloride)

Regulatory Contact: CanReg Inc. (representing Axcan Scandipharm Inc.)
440 North Lakeshore Drive
Mundelen, IL 60060

Applicant: Axcan Scandipharm Inc.
22 Inverness Center Parkway, Suite 310
Birmingham, AL 35242

Clinical Reviewer: Joette M. Meyer, Pharm.D.
Team Leader: Eileen Navarro Almario, M.D.
Division Director: Renata Albrecht, M.D.
Acting Office Director: Edward Cox, M.D., M.P.H.
**Regulatory Project
Manager:** Rebecca Saville, Pharm. D.

Submissions and Actions:

Original NDA:	September 28, 2001 (stamp date October 2, 2001)
FDA letter:	August 12, 2002 (not approvable letter, chemistry deficiencies)
Resubmission:	March 31, 2003 (stamp date April 2, 2003)
FDA letter:	October 2, 2003 (not approvable letter, chemistry deficiencies)
Resubmission:	March 27, 2006
PDUFA goal:	September 28, 2006

Related IND: _____

Type of Submission: Complete Response to Not Approvable Letter dated October 2, 2003
(a) correction of chemistry deficiencies
(b) proposed revisions to package insert reflecting recent discussions with DSPTP: _____
(c) new trade name of Pylera[™]

Materials Reviewed: NDA Action Package, including reviews, faxes and labeling.

Selected literature references

RECOMMENDATIONS:

- 1) The application for Pylera should be approved for the indication:

“PYLERA™ capsules (biscalcitrates, metronidazole, and tetracycline hydrochloride), in combination with omeprazole are indicated for the treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. The eradication of *Helicobacter pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**.)”

- 2) The **DOSAGE AND ADMINISTRATION** section should state:

“Each dose of PYLERA™ includes 3 capsules. Each dose of all 3 capsules should be taken 4 times a day, after meals and at bedtime for 10 days. Patients should be instructed to swallow the PYLERA™ capsules whole with a full glass of water (8 ounces). One omeprazole 20 mg capsule should be taken twice a day with PYLERA™ after the morning and evening meal for 10 days.

Table 6: Daily Dosing Schedule for PYLERA™ and Omeprazole

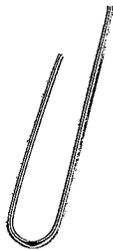
Time of dose	Number of capsules of PYLERA™	Number of capsules of Omeprazole 20 mg
After morning meal	3	1
After lunch	3	0
After evening meal	3	1
At bedtime	3	0

“Ingestion of adequate amounts of fluid, particularly with the bedtime dose, is recommended to reduce the risk of esophageal irritation and ulceration by tetracycline hydrochloride.”

- 3) The **HOW SUPPLIED** section will provide the following information on this fixed-combination product:

“PYLERA™ is supplied as a red opaque capsule containing 140 mg biscalcitrates, 125 mg metronidazole, and 125 mg tetracycline hydrochloride, with Axcan Pharma logo printed on body and HP, diagram of stomach and BMT printed on cap. PYLERA™ is supplied in bottles of 120 capsules.”

- 4) Other Issues:



2 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 1

A decision from USAN is pending as this time. A final decision from USAN does not need to be provided prior to an approval action. (The applicant has noted that to date they have received four positive responses in the USAN review process and that one additional response is currently pending.) If the proposed name of biskalcitrate is not accepted by USAN, the labeling will need to be changed to incorporate the accepted USAN name in the future when the USAN process is completed.

5) Postmarketing Commitments:

There are no post-marketing commitments.

Pediatric studies for ages 0-2 years of age are waived and studies for ages >2-16 years are deferred. Availability of an age appropriate formulation for younger patients will need to be addresses. Studies are deferred until September 30, 2011.

REGULATORY BACKGROUND AND SUMMARY OF APPLICATION:

(see reviews by Drs. Saville, Meyer, Navarro, Dionne, Jang and Holbert)

The original NDA 50-786 for Pylera¹ was submitted on September 28, 2001. A not approvable letter was issued due to chemistry deficiencies on August 12, 2002, and despite a Class 2 resubmission on March 31, 2003, a second not approvable letter again due to chemistry deficiencies was issued October 2, 2003. The [REDACTED] the manufacturing site for biskalcitrate, failed inspection on both occasions. The Class 2 submission of March 27, 2006 addressed and resolved these deficiencies.

According to Dr Holbert's review, the resubmission provides for a new manufacturer for the biskalcitrate drug substance, [REDACTED]. However, following inspection of [REDACTED] a 483 was issued on June 16, 2006 and Compliance recommended an action of withhold on August 3, 2006. The following deficiencies were noted, as reported by Dr. Holbert:

- The firm's use, qualification, calibration and maintenance of critical equipment;
- No SOPs for calibration or maintenance for manufacturing equipment;
- Conditions or practices exist where possible avenues of contamination of pharmaceutical products could occur;
- Not all elements of validation have been satisfied;
- Critical manufacturing processing points are not adequately controlled;
- Inadequate change control documentation;
No Annual Product Reviews; and
- Inadequate review and approval of equipment calibration.

¹ The original trade name proposed was Helicide, this was changed to Helizide on recommendation of DMETS. The company has now requested the name Pylera and this has been accepted by DMETS

The plant was reinspected during the week of September 18, 2006. Based on this second inspection, the field inspector and OC recommended approval on September 28, 2006.

Pylera is not being marketed at this time. It is approved in Canada (but is not marketed). Axcan is seeking approval in Europe. Pylera has never been taken off the market.

Clinical Development Program and Studies to Support Approval:

The clinical development program was conducted under IND and included Phase 1 clinical pharmacology studies that showed the AUC of bismuth and tetracycline in the fixed-drug combination was lower, and metronidazole was bioequivalent, when compared to AUCs achieved from individual drugs in the combination. Exposure was also reduced in the fed state compared to the fasted state. The difference is not considered clinically significant given the results of the Pylera clinical studies. In addition, the role of systemic vs. local drug concentrations has not been established in the treatment of *H. pylori* infection. Bismuth absorption was increased approximately 3-fold in the presence of omeprazole. This information will be included in labeling, but does not affect approval given that the Phase 3 studies used Pylera capsules and Pylera was found to be effective in clinical studies of *H. pylori*.

Phase 3 clinical studies:

Two clinical studies were submitted including an open-label comparative study conducted in North America (HPST99-CUS01) and a non-comparative study in Europe (HPST99-INT01).

The North American study compared omeprazole and Pylera (OBMT²) to omeprazole/ amoxicillin/ clarithromycin (OAC), a regimen approved for the treatment of *H. pylori*. The summary of this study that will be included in the **CLINICAL STUDIES** section of the Pylera labeling is presented below:

“Eradication of *Helicobacter pylori* in Patients with Active Duodenal Ulcer or History of Duodenal Ulcer Disease

“An open-label, parallel group, active-controlled, multicenter study in *Helicobacter pylori* positive patients with current duodenal ulcer or a history of duodenal ulcer disease was conducted in the United States and Canada.

“Patients were randomized to one of the following 10-day treatment regimens:

- Three (3) PYLERA™ capsules four times daily, after meals and at bedtime plus 20 mg omeprazole twice a day after breakfast and supper (**OBMT**).

² OBMT = omeprazole, bismalcaltrate, metronidazole, tetracycline

- Clarithromycin 500 mg plus 1000 mg amoxicillin plus 20 mg omeprazole twice a day before breakfast and supper (OAC).

“*H. pylori* eradication rates, defined as two negative ¹³C-urea breath tests performed at 4 and 8 weeks post-therapy are shown in Table 4 for OBMT and OAC. The eradication rates for both groups were found to be similar using either the Modified Intent-to-Treat (MITT) or Per Protocol (PP) populations.”

“Table 4. *Helicobacter pylori* Eradication at 8 Weeks after 10 Day Treatment Regimen Percent (%) of Patients Cured [95% Confidence Interval] (Number of Patients)

	Treatment Group		Difference
	OBMT*	OAC** ^c	
Per Protocol ^a	92.5% [87.8, 97.2] (n=110/120)	85.7% [76.9, 91.8] (n=108/126)	6.8 [-0.9, 14.5]
Modified Intent-to-Treat ^b	87.7% [82.2, 93.2] (n=121/138)	83.2% [77.0, 89.5] (n=114/137)	4.5 [-3.9, 12.8]

OBMT: omeprazole + PYLERA™ (bismalate / metronidazole / tetracycline HCl)

** OAC: omeprazole + amoxicillin + clarithromycin

^a Patients were included in the analysis if they had *H. pylori* infection documented at baseline, defined as a positive ¹³C-UBT plus histology or culture, had at least one endoscopically verified duodenal ulcer ≥ 0.3 cm at baseline or had a documented history of duodenal ulcer disease, and were not protocol violators. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the evaluable analysis as failures of therapy.

^b Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above, and had at least one documented duodenal ulcer at baseline or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as failures of therapy.”

^c Results for OAC treatment represent all isolates regardless of clarithromycin susceptibility. Eradication rates for clarithromycin susceptible organisms, as defined by an MIC ≤ 0.25 µg/mL, were 94.6% and 92.1% for the PP and MITT analysis, respectively. Eradication rates for clarithromycin non-susceptible organisms, as defined by an MIC ≥ 0.5 µg/mL, were 23.1% and 21.4% for the PP and MITT analysis, respectively.

In addition to the information presented from the Phase 3 North American comparative study, results of the non-comparative European study were reviewed. The European study was conducted in patients with non-ulcer dyspepsia (NUD); the eradication of *H. pylori* in the Per Protocol Analysis was 142/146 (97.3%) and in the Modified Intent to Treat Analysis, it is 158/170 (92.9%). These results are supportive of the findings in the controlled study.

Other supportive clinical data:

Approval of this 505(b)(2) application is supported by the agency’s previous finding of safety

and efficacy for Helidac, and published articles, summarized, in part, below.

Helidac® application, NDA 50-719

For comparison, information on Helidac® and Pylera regimens is presented in the table below (adapted from table in Dr Navarro's review):

Drug	Regimen	Drug Content	Daily Dose (mg)	Duration of Treatment	Efficacy rate in labeling (95% CI)
HELIDAC® * Bismuth subsalicylate Metronidazole Tetracycline	2 tablets QID	262.4 mg/ tablet	2100	14 days	Graham, comparative trial = 77% (61-89%). Cutler, non- comparative trial = 82% (70-92%). P&GP, comparative trial = 71% (60-83%), control 7% (0-16%).
	1 tablet QID	250 mg tablet	1000	14 days	
	1 capsule QID	500 mg capsule	2000	14 days	
H2-receptor antagonist	ulcer treatment dose			14 days	
PYLERA™ Bismuth subcitrate (biscalcitate) Metronidazole Tetracycline	(fixed combination) 3 capsules QID	(per capsule) 140 mg	1680	10 days	PP: 92.5% (87.8-97.2%) ITT: 87.7% (82.2-93.2%)
		125 mg	1500	10 days	
		125 mg	1500	10 days	
Omeprazole	1 tablet BID	20 mg	40**	10 days	

*Helidac® summary: bismuth subsalicylate tablets are chewable; H₂ receptor antagonist, ranitidine, was used by most patients in Graham and Cutler studies (active duodenal ulcer disease), no H₂ blocker was used in P&GP study (history of duodenal ulcer disease); efficacy was judged by eradication of *H. pylori* (defined as negative culture, histology, rapid urease or ¹³C breath test) at least 4 weeks following the end of treatment in the per protocol population

**Omeprazole 40 mg is QD approved for gastric ulcer treatment, omeprazole 20 mg QD is approved for duodenal ulcer treatment and GERD, higher doses have been used in patients with hypersecretory conditions (e.g. Zollinger-Ellison syndrome)

During the review of the Helidac application, the review team also examined the relationship of *Helicobacter pylori* eradication and recurrence of ulcer. This work established eradication as a validated surrogate for clinical recurrence of ulcer disease and was subsequently published by Hopkins et al³.

Review of Selected Literature References, Justification for Non-Inferiority Study Design:

³ Hopkins RJ, LS Girardi, EA Turney. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996;110(4):1244-52.

A number of publications summarize results of treatment with bismuth, metronidazole, and tetracycline (BMT), with or without omeprazole, for *H. pylori* infection. Two studies specifically report on the efficacy of OBMT compared to BMT; they conclude that OBMT is superior to BMT (see table below).

OBMT vs. BMT Eradication Rates

Publication	OBMT n/N (%)	BMT n/N (%)	Difference (OBMT- BMT) % [95% CI]	p-value
De Boer ⁴ Netherlands	53/54 (98.1%)	45/54 (83.3%)	14.8% [4.2, 25.4], ITT	0.02
Borody ⁵ Australia	122/125 (97.6%)	110/124 (88.7%)*	8.9%	0.006

Adapted from table in Dr. Navarro's review

*plus BMT plus famotidine (Pepcid, H₂-receptor antagonist)

Pylera is a fixed-combination drug product and thus under 21 CFR 300.50, it must be shown that "...each component makes a contribution to the claimed effect." Evidence is available from multiple articles published over the years that summarize the benefit of three-drug therapy over single drug or dual-drug treatment in *H. pylori*. The incremental benefit of each component has been demonstrated. The added benefit provided by the combination of drugs is summarized, for example, in the publication by Chiba⁶ et al. The authors identified 27 clinical trials, and reported the following pooled eradication rates for single (18.6%), double (48.2%) and triple (82.3%) therapy. The differences were statistically significant: $p < 0.0005$. Eradication rates for monotherapy with various drugs ranged from 0-37%. The eradication rate with bismuth was 19.6%. Dual therapy eradication rates ranged from 28% to 79%, and eradication with bismuth and metronidazole was 55.1%. Triple therapy for bismuth, metronidazole, and tetracycline yielded an eradication rate of 94.1%. The literature therefore also confirms the efficacy of the combination treatment for *H. pylori*, and demonstrates that each component makes a contribution to the claimed effect. The information from the literature, with specific examples from the Chiba, De Boer, and Borody studies, provides evidence that the combination of OBMT is effective in the treatment of *H. pylori* infection and that each component makes a contribution to the claimed effect.

In summary, the clinical and statistical reviewers have concluded that the omeprazole and Pylera regimen is effective, and that the efficacy of OBMT is supported by results from the clinical studies in the NDA, the agency's finding of safety and efficacy of Helidac, and multiple published studies evaluating drug efficacy in eradicating *H. pylori* that demonstrated:

⁴ De Boer W, Driessen W, Jansz A, et al. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. *Lancet* 1995;345:817-20

⁵ Borody TJ, Andrews P, Fracchia G, et al. Omeprazole enhances efficacy of triple therapy in eradicating *Helicobacter pylori*. *Gut* 1995;37:477-81.

⁶ Chiba N, et al. Meta-analysis of the efficacy of antibiotic therapy in eradicating *Helicobacter pylori*. *Am J Gastroenterol* 1992. 87(12):1716-1727.

- (a) Single drugs alone have very low efficacy
- (b) Double therapy has lower efficacy compared to three-drug therapy
- (c) Each antimicrobial agent contributes to the overall efficacy of the BMT regimen
- (d) Omeprazole, a proton pump inhibitor, increases the eradication rate achieved by BMT therapy based upon the findings from two published studies that show that OBMT is superior to BMT
- (e) Pylera is non-inferior to OAC, with a lower margin of 4%, this preserves at least half the difference seen in the Borody (8.9%) and DeBoer (14.8%) studies of OBMT vs. BMT. In addition, Dr. Meyer further notes in her review that “the efficacy against *H. pylori* is 0% for placebo⁷, less than 5% for monotherapy with a proton pump inhibitor (3-4% with omeprazole⁸, 2% with lansoprazole⁹), and 0% for amoxicillin alone¹⁰.”

Safety:

The adverse event profile of this regimen is summarized in the clinical reviews. There were 69 subjects in the Phase 1 studies and 324 patients in the Phase 3 studies who received Pylera. A pre-approval safety conference for this product was waived, with the concurrence of OSE, given that although bismalcaltrate is officially an NME, it is believed that toxicities with this entity (which is converted to potassium citrate, citric acid, and bismuth oxide upon ingestion) would be similar to other bismuth-containing compounds.

The three drugs within these combinations have been approved as individual drugs for various indications

- Metronidazole (NDA 12-623, Flagyl) was approved on July 18, 1963.
- Tetracycline was approved in 1957
- Bismuth salts include bismuth subsalicylate (Pepto-Bismol), a mucosal protectant available over-the-counter and used to treat diarrhea, nausea and indigestion (See 21 CFR 330.11 and 331.11).

Helidac[®], a co-package of bismuth subsalicylate, metronidazole, and tetracycline hydrochloride was approved August 15, 1996 (NDA 50-719). Helidac was also a 505(b)(2) application that relied on literature data; patient level data were requested and inspections of Dr. Graham's and Dr. Cutler's study sites were obtained. Results from these studies are included in the Helidac

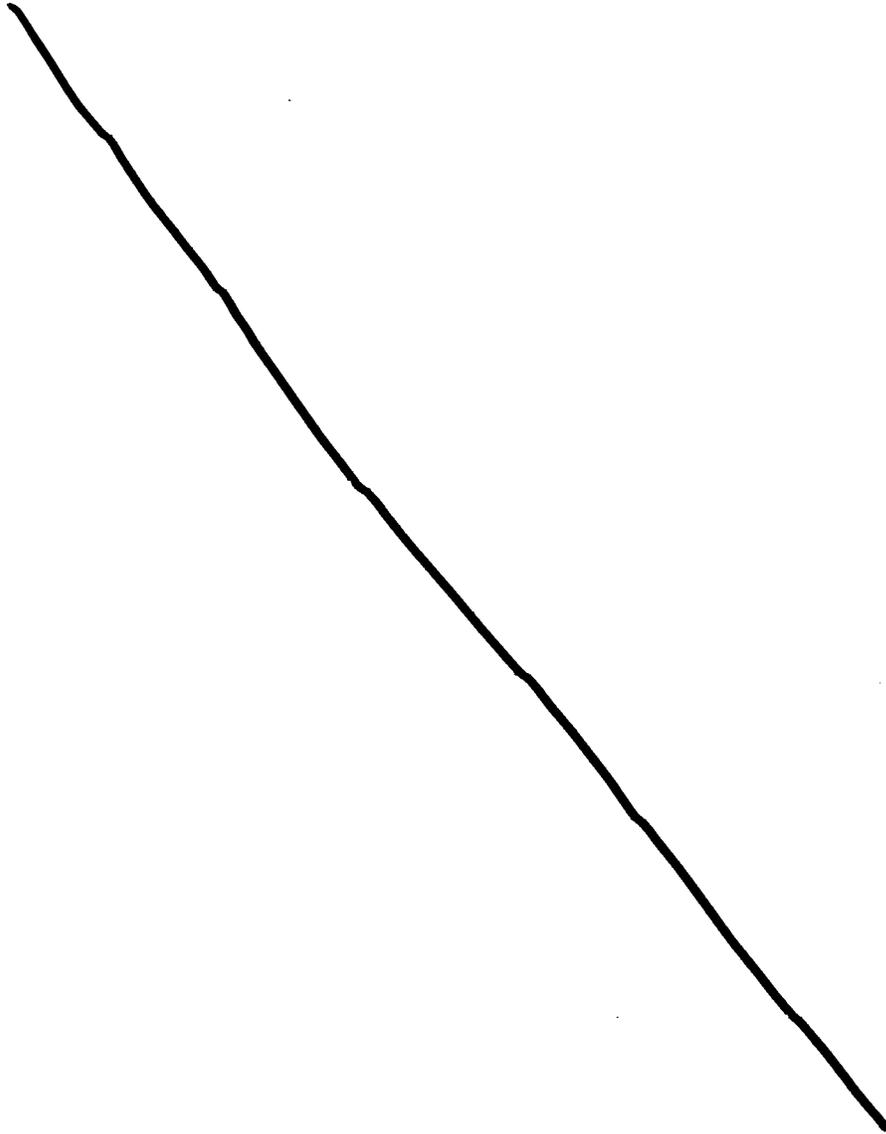
⁷ Peterson WL, Ciociola AA, Sykes DL, et al. Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating *H. pylori* and reducing ulcer recurrences. RBC *H. pylori* Study Group. *Aliment Pharmacol Ther* 1996;10:251-61.

⁸ Laine L, Johnson E, Suchower L, et al. US double-blind, controlled trials of omeprazole and amoxycillin for treatment of *Helicobacter pylori*. *Aliment Pharmacol Ther* 1998;12:377-82.

⁹ Schwartz H, Krause R, Sahba B, et al. Triple versus dual therapy for eradicating *Helicobacter pylori* and preventing ulcer recurrence: a randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. *Am J Gastroenterol* 1998;93:584-90.

¹⁰ Harford W, Lanza F, Arora A, et al. Double-blind, multicenter evaluation of lansoprazole and amoxicillin dual therapy for the cure of *Helicobacter pylori* infection. *Helicobacter* 1996;1:243-50.

product labeling.





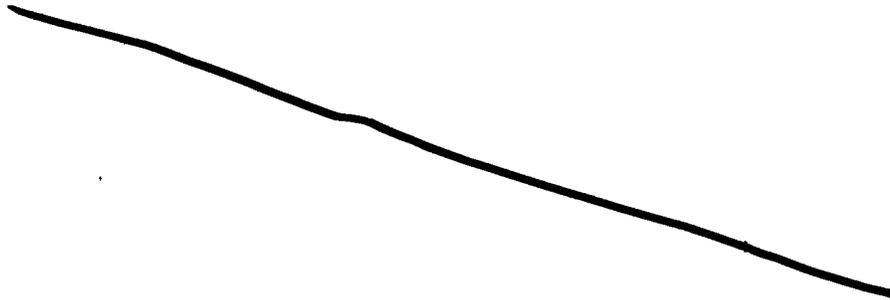
 1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 1



DSI inspections

DSI inspections were not conducted for this 505(b)(2) application. This application contains previously approved antibacterial agents, is supported by data from the literature, as well as the Agency's previous finding of safety and efficacy for Helidac (NDA 50-719, approved 1996), a product that contains bismuth subsalicylate, metronidazole and tetracycline. The company has conducted two clinical trials, one comparative and one non-comparative – no issues were identified during the course of review that would warrant a for-cause inspection.

Conclusion:

Pylera capsules (biscalcitrates, metronidazole, and tetracycline hydrochloride) should be approved for treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) in combination with omeprazole in order to eradicate *Helicobacter pylori*.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Edward Cox
9/28/2006 05:05:30 PM
MEDICAL OFFICER

Renata Albrecht
9/28/2006 05:13:59 PM
MEDICAL OFFICER

Medical Team Leader's Review
NDA 50-786, N-000, resubmitted 27 March 2006

Drug: Pylera[™] Capsules
(Biskalcitrate + Metronidazole + Tetracycline HCl)

Drug Identification:

Generic Name: Biskalcitrate + Metronidazole + Tetracycline HCl
Pharmacologic Category: Mucosal Protectant (Biskalcitrate) and
Antimicrobial (Metronidazole and Tetracycline)
Proposed Trade Name: Pylera Capsules
Formerly, Helizide[™], Helicide, Single-Triple
capsules

Molecular Formula: Biskalcitrate
 $\text{BiC}_{12}\text{H}_{14}\text{K}_5\text{O}_{17}$
Molecular Weight: 834.71 daltons
Dosage Form: Capsule containing Biskalcitrate 140 mg
(equivalent to 40 mg Bi_2O_3) + metronidazole 125
mg + tetracycline 125 mg
Dosage Regimen: 3 Pylera[™] capsules taken 4 times daily (after
meals and at bedtime) in combination with
omeprazole 20 mg twice a day
Route of Administration: Oral

General Information:

Regulatory Contact: CanReg Inc. (representing Axcan Scandipharm Inc.)
440 North Lakeshore Drive
Mundelen, IL 60060
Applicant: Axcan Scandipharm Inc. (formerly Axcan Pharma Inc.)
22 Inverness Center Parkway, Suite 310
Birmingham, AL 35242

Submission (and Action) Dates:

Original NDA: September 28, 2001
(nonapproved for chemistry deficiencies August 12, 2002)
Resubmission: March 21, 2003
(nonapproved for chemistry deficiencies October 2, 2003)
Second Resubmission: March 27, 2006
PDUFA Goal Date: September 27, 2006
Date Review Completed: August 16, 2006

I agree with Dr. Meyer's 2003 review of the original NDA that concludes noninferiority of omeprazole, bismuth, metronidazole and tetracycline (previously HELIZIDE[®], referred to hereinafter as PYLERA[®]) plus omeprazole to omeprazole, amoxicillin and clarithromycin (OAC) in *H. pylori* eradication in the single pivotal North American trial that enrolled patients with duodenal ulcer in the last five years.

***H. pylori* Eradication at Day 56 Visit
Per Protocol and Modified Intent-to-Treat Analyses**

<i>H. pylori</i> Eradicated Follow-up Visit	PYLERA	OAC	Difference (PYLERA – OAC)
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]*
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/126 (85.7) [79.6, 91.8]	6.8 [-0.9, 14]
Modified Intent-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

- 95% Confidence Interval for the difference in proportions (PYLERA- OAC) is calculated using normal approximation to binomial distribution

Dr. Meyer's review of a supportive non-comparative phase III international trial buttresses the efficacy demonstrated in the pivotal US trial, although the population of patients with *H. pylori* infection differed from those in the pivotal trial (non-ulcer dyspepsia vs duodenal ulcers). Under Section 505(b)(2) of the Food, Drug and Cosmetics Act, the applicant also referenced the FDA's finding of safety and effectiveness of one other bismuth, metronidazole, tetracycline combination with an H2 receptor antagonist (Helidac[®], NDA 50,719) in the eradication of *H. pylori*, and additional published literature to support the findings in the pivotal trial. The published literature was found sufficient by Dr. Meyer in

- a) providing support for the rationale for the combined use of PYLERA[®] and omeprazole in the eradication of *H. pylori*
- b) describing the contribution of each drug component to the efficacy of the PYLERA[®] regimen
- c) providing support for the efficacy of this combination from 31 literature articles in which PYLERA[®] therapy was used in various drug doses and durations for the treatment of *H. pylori* in various patient populations (non ulcer dyspepsia, patients with active gastric or duodenal ulcer, patients with a history of ulcer).

As discussed by Dr. Meyer, the efficacy outcomes achieved with PYLERA[®] (92.5%) are similar to the Per Protocol eradication rate outcomes achieved at 8 weeks post-treatment demonstrated with other FDA approved regimens (see table next page).

Efficacy of FDA-Approved *H. pylori* Treatment Regimens

Indication	Treatment Regimens	Dosage	Duration	Efficacy**
Alternative†	Amoxicillin	1 gm TID	14 days	66%, 77%
	Lansoprazole (Prevacid [®])	30 mg TID	14 days	
Primary therapy	Clarithromycin (Biaxin [®]) Omeprazole (Prilosec [®])	500 mg TID 40 mg QD, then 20 mg QD‡	14 days 14 days (Day 15-29)	64%, 74%
	Clarithromycin (Biaxin [®]) Amoxicillin Omeprazole (Prilosec [®])	500 mg BID 1 gm BID 20 mg BID, then 20 mg QD‡	10 days 10 days 10 days (Day 11-28)	78%, 78%, 90%
	Clarithromycin (Biaxin [®]) Amoxicillin Lansoprazole (Prevacid [®])	500 mg BID 1 gm BID 30 mg BID	10 days 10 days 10 days	84%
	Clarithromycin (Biaxin [®]) Amoxicillin Lansoprazole (Prevacid [®])	500 mg BID 1 gm BID 30 mg BID	14 days 14 days 14 days	86%, 92%
	Clarithromycin (Biaxin [®]) Amoxicillin Esomeprazole (Nexium [®])	500 mg BID 1 gm BID 40 mg QD	10 days 10 days 10 days	84%, 85%
	Clarithromycin (Biaxin [®]) Amoxicillin Rabeprazole (Aciphex [®])	500 mg BID 1 gm BID 20 mg BID	7 days 7 days 7 days	84% [^]
	Helidac[®] (Bismuth subsalicylate Metronidazole Tetracycline) H2-blocker*	2 - 525 mg tablets QID 250 mg QID 500 mg QID ulcer-treatment doses	14 days 14 days 14 days 28 days	77%, 82%, 71% [□]

** Per-protocol Eradication Rates in Phase III Trials

Evaluable patients were defined as having confirmed active or history of (within 2 years) duodenal ulcer disease and *H. pylori* infection at baseline and for whom results were available for the 4-6 week post-treatment visit

* Not included in Helidac[®] (bismuth subsalicylate, metronidazole, and tetracycline tablets/capsules packaged together)

□ In patients with a history of duodenal ulcer disease

† "or patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected"

‡ In patients with an ulcer present at the time of initiation of therapy

[^] evaluable patients were defined as having peptic ulcer disease (confirmed active or history of ulcer within 5 years) or asymptomatic non-ulcer disease and *H. pylori* infection at baseline and for whom results were available at the 6 week post-treatment visit

The Agency's finding of safety and efficacy of the first bismuth containing regimen, and also the first regimen with metronidazole and tetracycline as the active anti *H. pylori* drugs (HELIDAC[®], NDA 50-719, approved on 08/15/1996), was considered supportive of the efficacy of PYLERA[®]. The total daily doses of the individual drug components and the observed efficacy for these two regimens differ. PYLERA[®] is a fixed drug combination, used with a specific PPI at a specified dose. HELIDAC[®] was a co-packaged product containing individual tablets of the different drug components. The PPI drug and dose was not specified in the pivotal HELIDAC[®] efficacy trials. The HELIDAC[®] label

indicates that efficacy in *H. pylori* isolates with a metronidazole MIC of <8 µg/mL was 23/26 or 88.5% compared to an eradication of 4/7 or 57.8% of *H. pylori* isolates with an MIC ≥16 µg/mL, the metronidazole resistance breakpoint for anaerobes, but not *H. pylori*. For PYLERA[®], the applicant seeks labeling

Comparison of PYLERA[®] regimens evaluated by the FDA, and Applicant reported efficacy rates by MIC

Drug	Regimen	Drug Content	Daily Dose (mg)	Duration	Efficacy**
HELIDAC[®] Bismuth subsalicylate Metronidazole Tetracycline	2 tablets QID 1 tablet QID 1 tablet QID	525 mg tablet 250 mg tablet 500 mg tablet	4200 1000 2000	14 days	77%, 82%, 71% (23/26) 88.5% for Metronidazole MIC <8ug/ml (4/7) 57.8% for Metronidazole MIC >16ug/ml
H2-blocker* in "most patients"	ulcer-treatment doses	Not applicable			
PYLERA[®] Bismuth subcitrate Metronidazole Tetracycline	3 capsules QID	1 capsule with 140 mg 125 mg 125 mg	1680 1500 1500	10 days	92.5% (67/74) 91.8% for Metronidazole MIC <8ug/ml (42/52) 80.8% for Metronidazole MIC >16ug/ml
Omeprazole	1 tablet BID	20 mg	40*		

*2X the duodenal ulcer treatment dose of 20 mg QD, equivalent to the gastric ulcer treatment dose

** in the PP population, 4 weeks post EOT for HELIDAC

ACTIVITY OF BISMUTH and OMEPRAZOLE in PYLERA[®]

In addition to the cytoprotective effects of bismuth on the gastroduodenal mucosa, bismuth is claimed to possess anti *H. pylori* activity through various mechanisms including direct toxicity on membrane function, inhibition of protein and cell wall synthesis, inhibitions of urease enzyme activity, prevention of cytoadherence and ATP synthesis

In her review of the original submission, Dr. Meyer summarizes the supportive evidence provided that characterizes the individual contributions of the components of the fixed drug combination PYLERA[®], from, a meta-analysis of literature articles published between 1982 and 1990, performed by Chiba et. Al. in 1992.

Eradication Rates by Bismuth Treatment Regimen

Regimen	Number Eradicated / Number Treated	Eradication Rate (%)
Bismuth Alone	76 / 387	19.6 %
Bismuth + Metronidazole	65 / 118	55.1 %
Bismuth + Metronidazole + Tetracycline	191 / 203	94.1 %

From Chiba N, Rao BV, Rademaker JW, et al. Meta-analysis of the efficacy of antibiotic therapy in eradicating *Helicobacter pylori*. Am J Gastroenterol 1992;87:1716-27.

Dr. Meyer's review also summarizes the added benefit of omeprazole to bismuth triple therapy; as proposed in the PYLERA[®] treatment regimen, from the published literature. The regimens, study design and outcomes in the 2 published studies differ slightly from the proposed PYLERA[®] regimen and the pivotal studies establishing its efficacy. However, the evidence indicates that the addition of a PPI improves eradication when added to bismuth triple therapy.

BMT Eradication Rates with or without Addition of a PPI

Publication	PYLERA [®] n/N (%)	BMT n/N (%)	Difference (PYLERA [®] - BMT)% [95% CI]*	p-value
De Boer	53/54 (98.1%)	45/54 (83.3%)	14.8% [4.4, 27.3]	0.02
Borody	122/125 (97.6%)	110/124 (88.7%)	8.9%	0.006

From De Boer W, Driessen W, Jansz A, et al. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. Lancet 1995;345:817-20. Borody TJ, Andrews P, Fracchia G, et al. Omeprazole enhances efficacy of triple therapy in eradicating *Helicobacter pylori*. Gut 1995;37:477-81.

Dr. Meyer concludes that the addition of each antimicrobial agent appears to contribute to the overall efficacy of the BMT regimen and that the addition of a proton pump inhibitor (omeprazole) appears to increase the eradication rate achieved by BMT therapy. Note that the incremental efficacy rates for PYLERA[®] established over metronidazole containing regimens in the above literature refer to all stains of *H. pylori* regardless of metronidazole MIC.

The salient points from Dr. Meyer's 2003 summary of efficacy conclusions (p 32, Clinical and Statistical Review for New Drug Application # 50-786) are reproduced below:

" Summary of Efficacy

The applicant conducted one pivotal trial in North America (HPST99-CUS01) to document the efficacy of Helizide therapy plus omeprazole (OBMT). It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of Helizide plus omeprazole versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the Helizide versus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are above a non-inferiority margin of - 15% and provide evidence of the efficacy of Helizide therapy."

"Other findings include:

The rate of eradication in patients treated with OBMT having a pre-treatment bacterial isolate with a metronidazole MIC ≤ 8 µg/mL is similar to patients having an isolate with a metronidazole MIC ≥ 16 µg/mL in both the MITT and PP analyses. Conversely, in the OAC group the rate of eradication in patients whose bacterial isolates pre-treatment are resistant to clarithromycin (defined as an MIC ≥ 1 µg/mL) is statistically inferior to patients having a susceptible clarithromycin pre-treatment isolate.

- *No conclusions can be drawn regarding the rates of emerging resistance to either OBMT or OAC due to the few number of patients with culture results available post-treatment."*

"The results of the supportive data provide further evidence of the efficacy of Helizide therapy plus omeprazole (OBMT)

- The International trial (HPST99-INT01) demonstrates eradication rates (92.9% by MITT analysis and 97.3% by PP analysis) consistent with, and numerically greater than, the pivotal North American trial (87.7% by MITT analysis and 92.5% by PP analysis)
- Two pilot studies using BMT therapy administered as separate formulations in a blister pack with or without a PPI helped to refine the dosing regimen and treatment duration
- Four investigator-sponsored trials of Helizide therapy using a prototype Helizide capsule with or without a PPI demonstrate eradication rates similar to what was observed in the Phase III trials.
- The Agency's finding of safety and efficacy for Helidac[®] therapy (bismuth subsalicylate, metronidazole, tetracycline) plus an H₂-receptor antagonist.
- Literature data demonstrates incremental increases in eradication rates achieved with each component of bismuth triple therapy over bismuth alone (19.6% for bismuth, 55.1% for bismuth plus metronidazole, and 94.1% for bismuth plus metronidazole plus tetracycline). Addition of a proton pump inhibitor (omeprazole) to BMT therapy also increases eradication rates (by 8.9 to 14.8%) over use of BMT alone.
- The published efficacy of OBMT therapy for 7 to 14 days (mean 85.9%, range 65.5% to 100%) is similar to the pivotal North American trial (87.7%) as determined by MITT population analysis."

The original NDA submitted in 2003 was NOT APPROVED due to the failure of the manufacturing site in _____ to pass manufacturing inspections. The applicant subsequently pursued a resubmission of the NDA, and in a face to face pre NDA (February 8, 2006) meeting with the company, the reviewers provided the following advice specific to labeling of PYLERA[®] _____ The comments previously transmitted by facsimile to the applicant on February 6, 2006, are reproduced below

"The Division has reviewed the questions posed in your meeting package and has the following responses

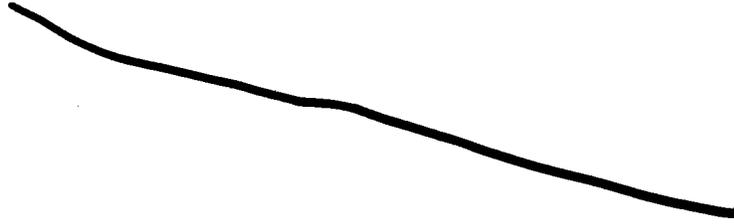
15 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

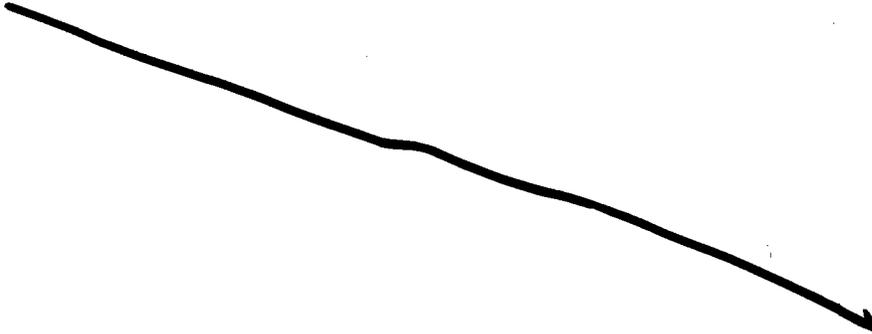
§ 552(b)(5) Draft Labeling

Withheld Track Number: Medical-2



Clinical Reviewers' Recommendation:

Should all outstanding chemistry deficiencies be addressed in this review cycle, I concur with Dr. Joette Meyer's recommendation that PYLERA[®] be approved for the treatment of *H. pylori*. Additional evidence demonstrating PYLERA[®] activity



Eileen Navarro, MD
Medical Team Leader
DSPIDP

Concurrence:
Renata Albrecht, MD
Director, DSPIDP

Cc: IND 50-786
Saville, Rebecca – PM
Willard, Diana – CPMS
Meyer, Joette – Clinical Reviewer
Higgins, Karen - Statistical Team Leader
Bala, Shukal – Micro TL
Dionne, Peter – Micro Reviewer

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Eileen Navarro
9/27/2006 05:52:15 PM
MEDICAL OFFICER

CLINICAL REVIEW

NDA: 50-786

Submission Date: 3/27/06

Date Review Completed: 9/27/06

Drug: Pylera™ Capsules (formerly Helizide™)
(Bismacitrate, Metronidazole, and Tetracycline Hydrochloride)

Regulatory Contact: CanReg Inc. (representing Axcan Scandipharm Inc.)
440 North Lakeshore Drive
Mundelen, IL 60060

Applicant: Axcan Scandipharm Inc.
22 Inverness Center Parkway, Suite 310
Birmingham, AL 35242

Primary Reviewer: Joette M. Meyer, Pharm.D.
Clinical Reviewer, DSPTP, OAP, CDER

Secondary Reviewer: Eileen Navarro Almario, M.D.
Medical Team Leader, DSPTP, OAP, CDER

Type of Submission: **Complete Response to Action Letter, Dated October 2, 2003**
Including proposed revisions to package insert reflecting recent discussions with DSPTP on [REDACTED] and new proposed trade name of Pylera™

I. REGULATORY BACKGROUND

The original NDA submission for Pylera (initially proposed as Helicide then modified to Helizide) was submitted on September 28, 2001. On August 12, 2002 the applicant received a Not Approvable Letter due primarily to deficiencies to the DMF and the drug substance. The applicant resubmitted the NDA on March 31, 2003. A Clinical Review of the NDA was completed and filed in DFS. The review concluded that Helizide capsules, when used in combination with omeprazole, are safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history) to eradicate *H. pylori*. However, on October 3, 2003 the applicant was issued a Not Approvable Letter, primarily due to GMP deficiencies found by the Office of Compliance upon inspection of the [REDACTED] facility in [REDACTED] the manufacturing site for bismacitrate. Discussion regarding the package insert for Helizide were initiated in September 2003 but not concluded due to the ongoing discussions regarding [REDACTED]

On January 25, 2006, the applicant submitted a meeting package for NDA 50-786 to discuss resubmission of the NDA and the [REDACTED]. On February 3, 2006 and on February 9, 2006 DSPTP sent correspondence to the applicant regarding the issue of [REDACTED]. On March 27, 2006 the applicant resubmitted NDA 50-786 with new CMC information, a response to the Division's correspondence regarding [REDACTED] and a revised package insert with the proposed trade name of Pylera.¹ No new clinical data were included in the resubmission.

The applicant proposes including a statement in the labeling regarding [REDACTED]
[REDACTED]
[REDACTED]

II. RECOMMENDATIONS ON APPROVABILITY FROM MEDICAL OFFICER'S REVIEW OF NDA 50-786

The following is reproduced from the Executive Summary of the original NDA review. Of note, the proposed trade name for Pylera at the time was "Helicide" and the active ingredient "biscalcitrates" was known as "biscalcitrates potassium."

In this submission, the applicant demonstrates the activity of Helicide capsules containing biscalcitrates potassium, metronidazole, and tetracycline hydrochloride plus omeprazole (Prilosec) capsules (abbreviated OBMT) in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (active or history). The efficacy of OBMT is compared to a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC regimen is an acceptable comparator since it consistently achieves eradication rates of approximately 70% or greater by Modified Intention-to-Treat (MITT) analysis and 80% or greater by Per Protocol (PP) analysis.

The applicant conducted one pivotal Phase III trial in North America (HPST99-CUS01) to document the efficacy of Helicide therapy plus omeprazole. It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -2.1% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are within the recommended range of $\pm 15\%$ and the *H. pylori* eradication rates for the OBMT treatment satisfies the efficacy criteria recommended in the FDA draft *H. pylori* Eradication Guidance.

Overall eradication rates for OBMT therapy in the non-comparative, supportive Phase III international trial are consistent with, although numerically higher than, the results obtained in the OBMT arm in the North American trial for the MITT (92.9% versus 87.7%) and PP (97.3% versus 92.5%) analyses, respectively. These results are similar to other drug therapy trials in which European rates of *H. pylori* eradication are often higher than those seen in North American trials.

Under Section 505(b)(2) of the FD&C Act, the applicant referenced the FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy containing bismuth subsalicylate, metronidazole, and tetracycline for the eradication of *H. pylori*), and literature articles on the efficacy of the combination of omeprazole, bismuth, metronidazole, and tetracycline (OBMT) therapy.

¹ Helicide as a proposed proprietary name was rejected by DMETS during the original NDA review. DMETS had no objections to use of the name "Helicide". With the resubmission the applicant is proposing to change the proprietary name from Helicide to "Pylera". DMETS accepted Pylera as a proprietary name.

In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any adverse event (AE). For both treatments gastrointestinal AEs were the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality, presumably due to the darkening effect of bismuth on the stool, is a commonly reported AE and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Although the safety data from the International trial are not pooled with the North American trial, the results are supportive of each other with regard to OBMT. The AEs reported for OBMT therapy in both the North American and International trials do not suggest that patients experience neurotoxicity related to bismuth after exposure to Helicide therapy.

Therefore, Helicide capsules (biscalcitrate potassium + metronidazole + tetracycline HCl), when used in combination with omeprazole, is safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. The recommendation is for approval of Helicide given as three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

Of Note: The Office of Compliance is recommending non-approval of this product due to a failed Prior Approval Inspection (PAI) for the biscalcitrate component.

Clinical Reviewer's Comment: In the North American trial, patients with a duodenal ulcer or history of an ulcer were randomized to Pylera plus omeprazole (OBMT) or omeprazole, amoxicillin, and clarithromycin (OAC). The International trial differed from the North American trial in that there was no comparator group and all patients received OBMT. Also, patients enrolled in the International trial all had gastrointestinal symptoms (i.e., non-ulcer dyspepsia). It was not necessary for these patients to have a history or current duodenal ulcer.

III. DATA INCLUDED IN THIS REVIEW

This review will focus on reanalysis of the [REDACTED] [REDACTED] previously reviewed with the original NDA (50-786) and additional literature information submitted by the applicant (as requested by DSPTP). In addition, the Reviewer will also address the issue of [REDACTED]. Supplemental information regarding other FDA-approved therapies is provided along with a labeling review of the Pylera package insert.

IV. SUMMARY OF FDA CORRESPONDENCE TO THE APPLICANT REGARDING

[REDACTED]

[REDACTED]

1. Letter dated February 3, 2006:

(1) Does the Agency agree that a pre-study MIC ≥ 32 $\mu\text{g/ml}$ is an acceptable breakpoint for defining [REDACTED] in *H. pylori*? If not, would the Agency comment on what would be considered acceptable?

We are not ready to accept a pre-study MIC ≥ 32 $\mu\text{g/mL}$ at this time because of the following:

- (a) An agreed-upon method for testing the [REDACTED] has currently not been established.
- (b) Agreed-upon [REDACTED] have currently not been established.
- (c) In addition, the mechanism of action that would support the activity and efficacy of a [REDACTED] is unclear.
- (d) Given the lack of standard testing methodology and established breakpoints, interpreting clinical trial results describing outcome in patients infected with [REDACTED] when treated with [REDACTED] regimens is challenging.
- (e) From the data presented, whether the difference in efficacy [REDACTED] compared to efficacy against [REDACTED] is clinically meaningful or not is unclear.

We agree that the distribution of [REDACTED] MICs shows a bi-modal distribution in the population. However, whether or not treatment failure occurs at a particular MIC is not clearly defined and may be dependent upon the treatment regimen administered, especially the dose and duration of treatment. For example, eradication rates may be lower for patients with *H. pylori* isolates having [REDACTED] (typically defined as an MIC ≥ 8 mcg/mL) treated with specific [REDACTED] regimens (e.g., dual therapy, bismuth-based triple therapy and PPI/metronidazole/amoxicillin) compared to those patients whose isolate has an MIC < 8 mcg/mL according to the literature. However, this difference in eradication rates can be surmountable by using more prolonged therapy (14 day treatment regimen) with the same [REDACTED] or by the addition of clarithromycin (PPI/metronidazole/clarithromycin).

In contrast to [REDACTED] clarithromycin has a standardized testing methodology, as well as CLSI-approved and FDA-labeled breakpoints for *H. pylori*. For clarithromycin, a clear separation between treatment success rates (i.e., clarithromycin-containing regimens achieve up to 90% eradication for clarithromycin-susceptible isolates vs. only 20% eradication for resistant isolates) has been established.

[REDACTED]

Furthermore, five regimens are FDA-approved that contain PPI/clarithromycin/amoxicillin, all of which are treatment-alternatives for patients regardless of the pre-treatment [REDACTED]

Lacking the information contained within points (a) through (e) above, we do not consider it acceptable at this time to set [REDACTED] *H. pylori*. Before we can determine whether a [REDACTED] MIC represents an acceptable breakpoint and whether a [REDACTED] can be used for treating [REDACTED] we would like you to provide the following information:

1. An approved method for testing [REDACTED] *H. pylori*. This method must be accepted by the scientific community and be reproducible in different laboratories. The method must also be acceptable to the Agency.
2. Rationale for the mechanism of [REDACTED] and how treatment with Helizide and omeprazole overcomes that mechanism.
3. Evidence that patients with MICs above a certain value, as determined by the agreed upon standardized method, have lower eradication rates compared to patients infected with isolates having lower MICs. Such information should include a discussion of what is considered a clinically and statistically-meaningful difference or loss of efficacy.
4. When you have determined the MIC breakpoint that demonstrates a clinically and statistically-meaningful difference in [REDACTED] this breakpoint should be applied to both arms of Study HPST99-CUS01. Compare results between the OBMT and OAC arms for patients with [REDACTED]. Furthermore, you should also include an analysis between OBMT and OAC for [REDACTED].
5. Evidence from a study that shows that OBMT is more efficacious in [REDACTED] than a regimen that has difficulties eradicating [REDACTED]. The choice of a comparator regimen can be discussed with the Agency in more detail. This study should show that OBMT has superior efficacy in eradication over the comparator.

(2) Does the Agency agree that the re-analysis of the HPST99-CUS01 data using a breakpoint of 32 µg/ml is acceptable, and that they would accept this analysis as part of the major amendment to the Helizide™ NDA?

No, please see answer to question (1), above.

(3) Would the Agency be open to the inclusion of the results of this analysis in the final labeling for Helizide™?

No, please see answer to question (1), above.

We would welcome the opportunity to discuss in more detail what information may result in labeling [REDACTED]

2. Letter dated February 9, 2006:

Regarding point #4 [in the February 3, 2006 letter] stating "When you have determined the MIC breakpoint that demonstrates a clinically and statistically-meaningful difference in [REDACTED] this breakpoint should be applied to both arms of Study HPST99-CUS01. Compare results between the OBMT and OAC arms for patients with [REDACTED]. Furthermore, you should also include an analysis between OBMT

and OAC for [REDACTED]
comment:

the Division has the following additional

*Clinical Reviewer's Comment: The original database for Study HPST99-CUS01 contained all of the pertinent information requested by DSPTP in this letter (i.e., [REDACTED] and *H. pylori* eradication in both the OAC and OBMT arms of the study); therefore, the applicant did not retest any isolates and was able to conduct the analysis as requested by DSPTP. The results are discussed in #4 in Section III below.*

V. SUMMARY AND REVIEW OF APPLICANT'S RESPONSE TO FDA COMMENTS REGARDING [REDACTED]

In the resubmission, the applicant has addressed the comments from the FDA correspondence of February 6 and 9, 2006. Below is a summary of their response, as well as additional information provided by the Reviewer.

Clinical Reviewer's Comment: In the following summary the term "[REDACTED]" is used to describe [REDACTED] using various MIC breakpoints as used in the literature and by the applicant. It should be noted that use of the term "[REDACTED]" by the Reviewer does not denote acceptance by DSPTP of the [REDACTED] method or MIC breakpoint for [REDACTED].

1. Provision of an approved method for testing [REDACTED] against *H. pylori*.

The applicant stated that the method used to determine [REDACTED] in Study HPST99-CUS01 conforms to the CLSI guidelines for testing of anaerobes (agar dilution method).² In addition, the applicant followed the CLSI guidelines for QC testing of *H. pylori* (ATCC strain 43504 with [REDACTED] of MIC 64 to 256 µg/mL). However, the applicant acknowledged that there is no FDA- or CLSI-approved [REDACTED] against *H. pylori*.

In contrast, the agar dilution method was approved by the CLSI (at that time NCCLS) for [REDACTED] against *H. pylori* in 1999.

² Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Sixteenth Informational Supplement. CLSI Document M100-S16, Vol. 26, No. 1, CLSI, Wayne, PA, January 2006.

2. Literature to support the mechanism of metronidazole resistance and how treatment with Helizide and omeprazole overcomes that mechanism.

The applicant carried out a literature search to determine the mechanism of action of metronidazole. In summary, the antimicrobial activity of metronidazole is dependent upon the reduction of its nitro moiety to the nitro anion radical and other compounds, including nitroso and hydroxylamine derivatives. The reduced products exert damaging effects on bacterial DNA. The primary nitroreductase thought to be responsible reduction of metronidazole in *H. pylori* is an oxygen-insensitivity NADPH nitroreductase, encoded by the *rdxA* gene.³ However, the distribution of metronidazole MICs in *H. pylori* is generally bimodal with large standard deviations, suggesting multiple drug targets.⁴ Many studies have shown that in *H. pylori* some metronidazole radicals may be produced by alternate reductases, resulting in strain-specific background susceptibility. In addition, high dose metronidazole (≥ 1000 mg) demonstrates efficacy in the presence of metronidazole resistance, suggests that at high doses the alternate nitroreductase pathways are able to reduce enough metronidazole to kill the bacteria.^{5,6,7,8}

The applicant also provided literature to support a potential mechanism for the antibacterial effects of omeprazole. Although not known for sure, the antibacterial activity of omeprazole is likely due to its structural similarity with antibiotics which are active against *H. pylori*, its inhibition of bacterial urease, or on a possible interaction with bacterial ATPases that regulate transmembrane ion flux. Omeprazole is known to have synergistic clinical activity with metronidazole.^{9,10} Its beneficial properties are also due to an antisecretory effect resulting in an increase in the pH of the stomach, which has been correlated with greater antibacterial activity of other antibiotics (e.g., clarithromycin and tetracycline).¹¹ Many randomized trials have shown that adding acid suppression to bismuth-base triple therapy increases the cure rate in susceptible, as well as resistant, strains.

³ Goodwin A, Kersulyte D, Sisson G, et al. Metronidazole resistance in *Helicobacter pylori* is due to null mutations in a gene (*rdxA*) that encodes an oxygen-insensitive NADPH nitroreductase. *Mol Microbiol* 1998;28:383-93.

⁴ Van der Wouden EJ, Thijs JC, Van Zwet AA. Metronidazole susceptibility in *Helicobacter pylori*. *Gastroenterology* 1999;117:1032-3.

⁵ Bayerdorffer E, Lonovics J, Dite P, et al. Efficacy of two difference dosage regimens of omeprazole, amoxicillin and metronidazole for the cure of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1999;13:1639-45.

⁶ Qureshi WA, Graham DY. Antibiotic-resistant *H. pylori* infection and its treatment. *Curr Pharm Des* 2000;6:1537-44.

⁷ Gene E, Clvet X, Azagra R, et al. Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: a meta-analysis. *Aliment Pharmacol Ther* 2003;17:1137-43.

⁸ Fischbach LA, van Zanten S, Dickson J. Meta-analysis: the efficacy, adverse events, and adherence related to first-line anti-*Helicobacter pylori* quadruple therapies. *Aliment Pharmacol Ther* 2004;20:1071-82.

⁹ Andersoen LP, Colding H, Kristiansen JE. Potentiation of the action of metronidazole on *Helicobacter pylori* by omeprazole and bismuth subcitrate. *Int J Antimicrob Agents* 2000;14:231-4.

¹⁰ Chen M, Jensen B, Zhai L, et al. Nizatidine and omeprazole enhance the effect of metronidazole on *Helicobacter pylori* in vitro. *Int J Antimicrob Agents* 2002;19:195-200.

¹¹ Megraud F, Lamouliatte H. Review article: the treatment of refractory *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2003;17:1333-43.

The applicant provided several potential mechanisms whereby treatment with Helizide plus omeprazole may overcome metronidazole resistance:

- The anti-bacterial action of tetracycline, bismuth, and omeprazole is not expected to be impacted by the metronidazole resistance phenotype, which is associated with mutant nitroreductase enzymes) since their mechanism of action depends on alternative cellular pathways.
- The activity of metronidazole may be enhanced by the presence of bismuth and omeprazole:
 - By compromising the glycocalyx-cell wall and thus increasing cell permeability, bismuth may allow for higher concentrations of metronidazole to enter the bacterial cell¹²
 - By interfering with efflux pumps, both bismuth and omeprazole could result in higher intracellular concentrations of metronidazole
 - In vitro data suggest that metronidazole and bismuth and metronidazole and omeprazole demonstrate synergistic antibacterial activity
- Resistance to metronidazole may be overcome at higher concentrations of metronidazole (seen with doses ≥ 1000 mg).

3. Evidence that patients with MICs above a certain value, as determined by the agreed upon standardized method, have lower eradication rates compared to patients infected with isolates having lower MICs, including a discussion of what is considered a clinically and statistically-meaningful difference or loss of efficacy.

The applicant carried out a literature search to address the prevalence of metronidazole resistance in the United States, and correlations between pre-treatment MIC values and clinical outcome and comparisons of triple (BMT) therapy versus quadruple (BMT plus a proton pump inhibitor).

The applicant concluded the overall rate of metronidazole resistance in the US is around 26% (based upon an MIC breakpoint of 8 $\mu\text{g}/\text{mL}$) and there is substantial proof and agreement that pre-treatment metronidazole resistant *H. pylori* has an important negative impact on clinical outcome; however, the extent of the impact is highly dependent on the treatment regimen.

The applicant was not able to provide a discussion of what is considered a clinically or statistically-meaningful difference or loss of efficacy between

¹² Stratton CW, Warner RR, Coudron PE, et al. Bismuth-mediated disruption of the glycocalyx-cell wall of *Helicobacter pylori*: ultrastructural evidence for a mechanism of action for bismuth salts. J Antimicrob Chemother 1999;43:659-66.

susceptible and resistant isolates. However multiple meta-analyses found by the applicant in the literature using a pre-treatment breakpoint of 8 µg/mL, showed a 5% to 43% reduction in efficacy for patients with pre-treatment metronidazole resistant isolates treated with various dual and triple therapies containing metronidazole.^{6,13,14,15,16,17}

The Clinical Reviewer conducted the following analysis shown in Table 1A, which evaluates the difference in efficacy between metronidazole “resistant” (MIC ≥ 16 µg/mL) and “susceptible” isolates (MIC ≤ 8 µg/mL) for various therapies containing metronidazole. The data are limited to US-based studies conducted under IND (i.e., protocols reviewed by DSPTP), in ulcer patients using the agar dilution method to determine metronidazole susceptibility (defined as MIC ≤ 8 µg/mL in all studies). By limiting the analysis to only the following studies, it is possible to eliminate possible confounders present in the applicant’s analysis, such as inclusion of patients with non-ulcer dyspepsia (may have higher overall eradication rates than the ulcer population), European data (also known to produce higher overall eradication rates) and use of the E-test (results do not always correlate with those obtained by the agar dilution method).

As shown in Table 1A, all regimens are less effective against metronidazole “resistant” isolates (MIC ≥ 16 µg/mL) compared to “susceptible” isolates (MIC ≤ 8 µg/mL), although the loss in efficacy appears less with Pylera plus omeprazole (OBMT) than with the other regimens.

¹³ Graham DY, de Boer WA, Tytgat GN. Choosing the best anti-*Helicobacter pylori* therapy: effect of antimicrobial resistance. *Am J Gastroenterol* 1996;91:1072-6.

¹⁴ Megraud F, Lehn N, Lind T, et al. Antimicrobial susceptibility testing of *Helicobacter pylori* in a large multicenter trial: the MACH 2 study. *Antimicrob Agents Chemother* 1999;43:2747-52.

¹⁵ Lind T, Megraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of *Helicobacter pylori* with 1-week triple therapies. *Gastroenterology* 1999;116:248-53.

¹⁶ Dore MP, Leandro G, Realdi G, et al. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of *Helicobacter pylori* therapy: a meta-analytical approach. *Dig Dis Sci* 2000;45:68-76.

¹⁷ Katelaris PH, Forbes GM, Talley NJ, et al. A randomized comparison of quadruple and triple therapies for *Helicobacter pylori* eradication. The QUADRATE Study. *Gastroenterology* 2002;123:1763-9.

TABLE 1A
Summary of Eradication Rates by Metronidazole MIC in US-Based Studies Conducted under IND

Therapy	Origin of Study	Overall Eradication ¹	Eradication by Metronidazole MIC In the ITT Population ²		
			Metronidazole MIC ≤ 8 µg/mL	Metronidazole MIC ≥ 16 µg/mL	Difference (“Susceptible” minus “Resistant”)
OBMT (Pylera plus omeprazole) x 14 days	Pylera NDA (US and Canada)	PP 92.5% (111/120) ITT 87.7% (121/138)	91.8% (67/74)	80.8% (42/52)	11%
BMT (Helidac) x 14 days (No H ₂ included)	Helidac Label (US)	PP 71% (40/56) ITT 72% (41/57)	88.5% (23/26)	57.1% (4/7) <i>Small sample size and unreliable estimate</i>	--*
PCM x 7 days	In support of NDA ³ (US)	Study A: PP 76% ITT 73% Study B: PP 85% ITT 81%	Study A: 82% (70/85)	Study A: 63% (22/35)	Study A: 19%
			Study B: 87% (62/71)	Study B: 73% (19/26)	Study B: 14%
CM x 7 days		PP 73% ITT 68%	74% (57/77)	58% (15/26)	16%
OAC x 14 days	Pylera NDA (US and Canada)	PP 85.7% (108/126) ITT 83.2% (114/137)	84.5% (60/71)	81.8% (36/44)	2.7%

O = omeprazole; B = bismuth; M = metronidazole; T = tetracycline; P = pantoprazole; C = clarithromycin; A = amoxicillin
 * Sample size of metronidazole resistant isolates in the BMT study was too small to allow a reliable estimate
¹ duodenal ulcer patients (active and/or history)
² agar dilution method

³ Studies designed under IND with DSPIDP ; NDA never submitted due to ineffective therapy (Reference: Camargo MC, et al. Helicobacter 2004;9(4):626-42)

**Appears This Way
On Original**

In Table 1B the difference in efficacy between “resistant” (MIC \geq 16 $\mu\text{g/mL}$) and “susceptible” (MIC \leq 8 $\mu\text{g/mL}$) isolates is calculated by comparing OBMT (Pylera therapy) to the other regimens listed in Table 1A. No comparison was conducted using the data for resistant isolates in the BMT (Helidac) study, due to the small sample size and instability in the estimate of efficacy. For all comparisons conducted, the difference in efficacy is greater for metronidazole “resistant” isolates compared to “susceptible” isolates, with the exception of the comparisons between PCM and CM.

TABLE 3B
Comparison of Difference in Efficacy for Various Metronidazole-Containing Regimens
Evaluated for Metronidazole Susceptible (MIC \leq 8 $\mu\text{g/mL}$) and Resistant (MIC \geq 16
 $\mu\text{g/mL}$) Isolates

Regimen Comparison	Difference in Efficacy (%)	
	Metronidazole MIC \leq 8 $\mu\text{g/mL}$	Metronidazole MIC \geq 16 $\mu\text{g/mL}$
OBMT vs. BMT	3.3%	--*
OBMT vs. PCM (Study A)	9.8%	17.8%
OBMT vs. PCM (Study B)	4.8%	7.8%
OBMT vs. CM	17.8%	22.8%
BMT vs. PCM (Study A)	6.5%	--*
BMT vs. PCM (Study B)	1.5%	--*
BMT vs. CM	14.5%	--*
PCM (Study A) vs. CM	8%	5%
PCM (Study B) vs. CM	13%	8%

O = omeprazole; B = bismuth; M = metronidazole; T = tetracycline; P = pantoprazole; C = clarithromycin; A = amoxicillin; OBMT = Pylera plus omeprazole

* Sample size of metronidazole resistant isolates in the BMT study was too small to allow a reliable estimate

In summary, using the agar dilution method there appears to be an effect of metronidazole resistance (using a breakpoint of 16 $\mu\text{g/mL}$) on microbiologic efficacy for regimens containing metronidazole; however, the clinical and statistical significance of the magnitude of the effect is not known.

5 Page(s) Withheld

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

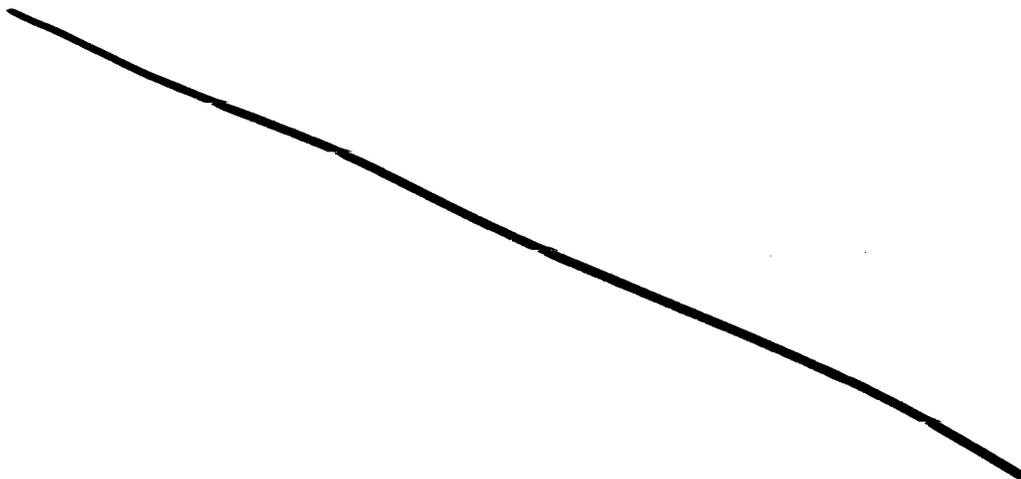
§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 3

As noted previously by the Clinical Reviewer, possible confounders are present when data from the literature are summarized broadly, as in Table 6, due to the inclusion of patients with non-ulcer dyspepsia (may have higher overall eradication rates than the ulcer population), European data (also known to produce higher overall eradication rates) and use of the E-test (results do not always correlate with those obtained by the agar dilution method). Therefore, the most appropriate comparison would be between BMT and OBMT in US-based studies conducted under IND, which is shown in Table 7 (a subset of Table 1A, shown above). The results of this analysis show that overall OBMT is more effective against metronidazole "resistant" (MIC \geq 16 μ g/mL) isolates (81%) compared to BMT (57%). However, the data is not definitive since, as noted previously, the BMT sample size was small and the estimate of efficacy is unstable.

TABLE 7



O = omeprazole; B = bismuth; M = metronidazole; T = tetracycline

* Sample size of metronidazole resistant isolates in the BMT study was too small to allow a reliable estimate

VI. SUMMARY OF APPLICANT'S DATA FOR CLARITHROMYCIN RESISTANCE

Although the applicant did not focus their attention on the efficacy of Pylera plus omeprazole against clarithromycin-resistant organisms, they do note in their resubmission that "the data [from Study HPST99-CUS01] support the efficacy of [Pylera] therapy in clarithromycin-resistant strains." As seen in Table 4 above, the efficacy of OBMT (Pylera plus omeprazole) against clarithromycin-resistant isolates is 77% (10/13) in the ITT population compared to 21% (3/14) for patients receiving OAC with clarithromycin-

resistant isolates.

Unlike metronidazole, CLSI approved a susceptibility testing method and susceptibility breakpoints for clarithromycin in 1999. In addition, and there is a clear correlation between microbiologic resistance to clarithromycin and clinical failure. Much data exists documenting the disparity between the efficacy of clarithromycin-containing regimens against clarithromycin-susceptible versus resistant isolates and the overall poor efficacy against clarithromycin-resistant isolates, as shown in Table 8 (created by the Reviewer).

All regimens in the table are FDA-approved and the data was obtained from the package inserts for clarithromycin, lansoprazole, esomeprazole, and rabeprazole.

TABLE 8
Summary of Efficacy by Clarithromycin Susceptibility for FDA Approved Regimens

Regimen	Efficacy*		Difference in Efficacy
	Clarithromycin "Susceptible" Isolates	Clarithromycin "Resistant" Isolates	"Susceptible" minus "Resistant"
OC x 14 days	72/108 (66.7%)	0/4 (0%)	66.7%
OAC x 10 days	153/171 (89.5%)	4/14 (28.6%)	60.9%
LAC x 14 days	105/112 (93.7%)	6/17 (35.3)	58.4%
LAC x 10 days	40/42 (95.2%)	1/4 (25%)	70.2%
EAC x 10 days	162/182 (89%)	13/29 (44.8%)	44.2%
RAC x 7 days	103/129 (79.8%)	5/16 (31.3%)	48.5%
RAC x 10 days	111/133 (83.4%)	1/9 (11.1%)	72.3%

O=omeprazole; C=clarithromycin; A=amoxicillin; L=lansoprazole; E=esomeprazole; R=rabeprazole

*Resistance was defined by an MIC of ≥ 2 $\mu\text{g/mL}$ in the OC, OAC, and LAC studies, reflecting the NCCLS recommendations for a tentative breakpoint at the time the studies were conducted.¹⁸ A clarithromycin resistance breakpoint of MIC of ≥ 1 $\mu\text{g/mL}$ was accepted by the NCCLS in 1999 and this new breakpoint was applied to the EAC and RAC studies.

Clinical Reviewer's Comment: For comparison, the efficacy against H. pylori is 0% for placebo¹⁹, less than 5% for monotherapy with a proton pump inhibitor (3-4% with omeprazole²⁰, 2% with lansoprazole²¹), and 0% for amoxicillin alone²².

¹⁸ National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL, January 11-13, 1998.

¹⁹ Peterson WL, Ciociola AA, Sykes DL, et al. Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating *H. pylori* and reducing ulcer recurrences. RBC *H. pylori* Study Group. *Aliment Pharmacol Ther* 1996;10:251-61.

²⁰ Laine L, Johnson E, Suchower L, et al. US double-blind, controlled trials of omeprazole and amoxicillin for treatment of *Helicobacter pylori*. *Aliment Pharmacol Ther* 1998;12:377-82.

²¹ Schwartz H, Krause R, Sahba B, et al. Triple versus dual therapy for eradicating *Helicobacter pylori* and

4 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 3

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joette Meyer
9/27/2006 10:36:06 AM
MEDICAL OFFICER

Eileen Navarro
9/27/2006 05:17:24 PM
MEDICAL OFFICER

**ADDENDUM TO
Clinical and Statistical Review for
New Drug Application # 50-786**

Drug: Pylera™ Capsules
(formerly known as Helicide and Single Triple Capsule):
Biscalcitrates + Metronidazole + Tetracycline HCl

Date of Review: September 27, 2006

Clinical Reviewer's Comment: This review is being amended following the resubmission of NDA 50-786 (dated March 27, 2006).

It should be noted that under Section 505(b)(2) of the FD&C Act, the applicant referenced the FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy containing bismuth subsalicylate, metronidazole, and tetracycline for the eradication of H. pylori), and literature articles on the efficacy of the combination of omeprazole, bismuth, metronidazole, and tetracycline (OBMT) therapy.

This version of the Clinical and Statistical Review supersedes any previous versions.

**ADDENDUM TO
Clinical and Statistical Review for
New Drug Application # 50-786**

Drug: Pylera™ Capsules
(formerly known as Helicide and Single Triple Capsule)
Bismal citrate + Metronidazole + Tetracycline HCl

Date of Review: September 27, 2006

Clinical Reviewer's Comment: This review is being amended following the resubmission of NDA 50-786 (dated March 27, 2006).

It should be noted that under Section 505(b)(2) of the FD&C Act, the applicant referenced the FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy containing bismuth subsalicylate, metronidazole, and tetracycline for the eradication of H. pylori), and literature articles on the efficacy of the combination of omeprazole, bismuth, metronidazole, and tetracycline (OBMT) therapy.

This version of the Clinical and Statistical Review supersedes any previous versions.

Clinical and Statistical Review for New Drug Application # 50-786

Drug: Helicide® (Single Triple Capsule)
Biscalcitrates potassium + Metronidazole + Tetracycline HCl

Applicant's Proposed Indication: Helicide® Capsules (biscalcitrates potassium, metronidazole, and tetracycline hydrochloride), in combination with omeprazole are indicated for the eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease (active or by history). The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.

General Information:

Regulatory Contact: CanReg Inc. (representing Axcan Scandipharm Inc.)
4 Innovation Drive
Dundas, Ontario
L9H 7P3
(905) 689-3980

Applicant: Axcan Scandipharm Inc. (formerly Axcan Pharma Inc.)
597 Laurier Boulevard
Mont-Saint-Hilaire, QC
Canada J3H 6C4
Telephone: (450) 467-5138
Fax: (450) 467-5857

Submission/Review Dates:

Date of Submission: September 28, 2001; July 8, 2002;
September 26, 2002
Date of Receipt: October 2, 2001; July 10, 2002; September 27, 2002
Date Review Begun: May 8, 2002
Date Review Completed: October 31, 2002

Drug Identification:

Generic Name: Biscalcitrates potassium + Metronidazole + Tetracycline HCl
Pharmacologic Category: Mucosal Protectant (Biscalcitrates potassium) and Antimicrobial (Metronidazole and Tetracycline)
Proposed Trade Name: Helicide®
Molecular Formula: Biscalcitrates potassium
(BiC₁₂H₁₀K₅O₁₅)₆ or (BiC₁₂H₁₀K₅O₁₆)₆
Molecular Weight: daltons
Dosage Form: Capsule containing biscalcitrates 140 mg + metronidazole 125 mg + tetracycline 125 mg
Route of Administration: Oral

TABLE OF CONTENTS

EXECUTIVE SUMMARY	i
I. RECOMMENDATIONS.....	1
A. <i>Recommendations on Approvability</i>	<i>i</i>
B. <i>Recommendations on Phase IV Studies and Risk Management Steps</i>	<i>ii</i>
II. SUMMARY OF CLINICAL FINDINGS.....	11
A. <i>Brief Overview of the Clinical Development Program</i>	<i>ii</i>
B. <i>Efficacy</i>	<i>iii</i>
1. <i>North American Trial (Protocol HPST99-CUS01)</i>	<i>iii</i>
2. <i>Comparison With Other FDA-approved Regimens</i>	<i>iv</i>
C. <i>Safety</i>	<i>vi</i>
1. <i>North American Trial (Protocol HPST99-CUS01)</i>	<i>vii</i>
D. <i>Dosing</i>	<i>viii</i>
E. <i>Special Populations</i>	<i>viii</i>
1. <i>Efficacy</i>	<i>ix</i>
2. <i>Safety</i>	<i>ix</i>
CLINICAL/STATISTICAL REVIEW.....	10
I. INTRODUCTION/BACKGROUND.....	10
A. <i>Overview of Drug, Dosage, and Indications</i>	<i>10</i>
B. <i>Important Milestones in Product Development</i>	<i>10</i>
C. <i>Other Relevant Information</i>	<i>11</i>
II. SUMMARY OF CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEW DISCIPLINES	11
A. <i>Chemistry</i>	<i>11</i>
B. <i>Pharmacology/Toxicology</i>	<i>11</i>
C. <i>Clinical Pharmacology/Biopharmaceutics</i>	<i>12</i>
D. <i>Microbiology</i>	<i>13</i>
III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS.....	14
A. <i>Pharmacokinetics</i>	<i>14</i>
B. <i>Pharmacodynamics</i>	<i>14</i>
IV. DESCRIPTION OF CLINICAL DATA AND SOURCES	16
A. <i>Overall Data</i>	<i>16</i>
B. <i>Table of Clinical Trials</i>	<i>16</i>
V. CLINICAL REVIEW METHODS.....	17
A. <i>Structure of the Review</i>	<i>17</i>
B. <i>Overview of Materials Consulted in Review</i>	<i>17</i>
C. <i>Overview of Methods Used to Evaluate Data Quality and Integrity</i>	<i>17</i>
D. <i>Evaluation of Financial Disclosure</i>	<i>18</i>
VI. INTEGRATED SUMMARY OF EFFICACY (ISE).....	19
A. <i>Brief Statement of Efficacy Conclusions</i>	<i>19</i>
B. <i>General Approach to Efficacy Review</i>	<i>19</i>
C. <i>Synopsis of Phase III Efficacy Results</i>	<i>19</i>
1. <i>North American Trial (HPST99-CUS01)</i>	<i>19</i>
2. <i>International Trial - Protocol HPST99-INT01</i>	<i>26</i>
D. <i>Other Supportive Efficacy Data</i>	<i>28</i>
1. <i>Pilot Studies</i>	<i>28</i>
2. <i>Investigator Sponsored Trials</i>	<i>28</i>
3. <i>Helidac NDA</i>	<i>29</i>
4. <i>Literature Review - Contribution of Each Drug to Efficacy</i>	<i>30</i>
5. <i>Literature Review - Efficacy of OBT Therapy</i>	<i>32</i>
E. <i>Summary of Efficacy</i>	<i>33</i>
VII. INTEGRATED SUMMARY OF SAFETY (ISS).....	35
A. <i>Brief Statement of Safety Conclusions</i>	<i>35</i>
B. <i>Description of Drug Exposure</i>	<i>35</i>

C. <i>Methods and Specific Findings of Safety Review</i>	35
1. Overview of Adverse Events	36
2. Adverse Events by Relationship to Treatment	41
3. Adverse Events by Subgroup (Age, Gender and Ethnicity)	41
4. Discontinuations from Study Due to Adverse Events	48
5. Deaths	50
6. Non-Fatal Serious Adverse Events	50
7. Pregnancy	51
8. Clinical Laboratory Evaluations	51
9. Vital Sign And Physical Findings Related to Safety	52
10. Clinical Pharmacology Studies	52
D. <i>Summary of Safety</i>	53
VIII. DOSING, REGIMEN, AND ADMINISTRATION ISSUES	54
IX. USE IN SPECIAL POPULATIONS	55
A. <i>Efficacy</i>	55
B. <i>Safety</i>	55
X. CONCLUSIONS AND RECOMMENDATIONS	55
A. <i>Conclusions</i>	55
B. <i>Recommendations</i>	56
APPENDIX 1 – Literature Table (Efficacy of obmt therapy).....	58
APPENDIX 2 – Additional Safety Tables for North American Trial (HPST99-CUS01) ...	60
APPENDIX 3 – Additional Safety Tables for International Trial (HPST99-INT01)	77
APPENDIX 4 – Individual Review of North American Trial (HPST99-CUS01)	83
I. CLINICAL AND STATISTICAL REVIEW OF NORTH AMERICAN TRIAL (HPST99-CUS01)	84
A. <i>Investigators and Study Administrative Structure</i>	84
B. <i>Study Objectives</i>	84
C. <i>Investigational Plan</i>	85
D. <i>Schedule of Visits</i>	86
E. <i>Inclusion Criteria</i>	88
F. <i>Exclusion Criteria</i>	88
G. <i>Patient Removal</i>	89
H. <i>Other Study Design Features</i>	89
I. <i>Diagnostic Methods</i>	90
J. <i>Efficacy Assessments</i>	90
K. <i>Statistical Analyses and Evaluability Criteria</i>	91
L. <i>Results</i>	93
1. <i>Investigators</i>	93
2. <i>Patient Accountability</i>	94
3. <i>Demographic Characteristics</i>	98
4. <i>Compliance Results</i>	100
5. <i>Eradication</i>	100
6. <i>Evaluability Status</i>	105
7. <i>Susceptibility</i>	107
8. <i>Safety Analyses</i>	108
M. <i>Reviewers’ Conclusions of Study HPST99-CUS01</i>	108
APPENDIX 5 – Proposed Label	109

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations on Approvability

In this submission, the applicant demonstrates the activity of Helicide capsules containing biscalcitrates potassium, metronidazole, and tetracycline hydrochloride plus omeprazole (Prilosec) capsules (abbreviated OBMT) in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (active or history). The efficacy of OBMT is compared to a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC regimen is an acceptable comparator since it consistently achieves eradication rates of approximately 70% or greater by Modified Intention-to-Treat (MITT) analysis and 80% or greater by Per Protocol (PP) analysis.

The applicant conducted one pivotal Phase III trial in North America (HPST99-CUS01) to document the efficacy of Helicide therapy plus omeprazole. It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -2.1% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are within the recommended range of $\pm 15\%$ and the *H. pylori* eradication rates for the OBMT treatment satisfies the efficacy criteria recommended in the FDA draft *H. pylori* Eradication Guidance.

Overall eradication rates for OBMT therapy in the non-comparative, supportive Phase III international trial are consistent with, although numerically higher than, the results obtained in the OBMT arm in the North American trial for the MITT (92.9% versus 87.7%) and PP (97.3% versus 92.5%) analyses, respectively. These results are similar to other drug therapy trials in which European rates of *H. pylori* eradication are often higher than those seen in North American trials.

Under Section 505(b)(2) of the FD&C Act, the applicant referenced the FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy containing bismuth subsalicylate, metronidazole, and tetracycline for the eradication of *H. pylori*), and literature articles on the efficacy of the combination of omeprazole, bismuth, metronidazole, and tetracycline (OBMT) therapy.

In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any adverse event (AE). For both treatments gastrointestinal AEs were the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality, presumably due to the darkening effect of bismuth on the stool, is a commonly reported AE and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Although the safety data from the International trial are not pooled with the North American trial, the results are supportive of each other with regard to OBMT. The AEs reported for OBMT therapy in both the North American and International trials do not suggest that patients experience neurotoxicity related to bismuth after exposure to Helicide therapy.

Therefore, Helicide capsules (biscalcitrates potassium + metronidazole + tetracycline HCl), when used in combination with omeprazole, is safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. The recommendation is for approval of Helicide given as three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

Of Note: The Office of Compliance is recommending non-approval of this product due to a failed Prior Approval Inspection (PAI) for the biscalcitrates component.

B. Recommendations on Phase IV Studies and Risk Management Steps

There are no Phase IV commitments recommended at this time.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Development Program

The worldwide clinical development program for Helicide in combination with omeprazole for the eradication of *H. pylori* includes:

- two Phase I (drug-drug interaction) studies
- two Phase III studies (HPST99-CUS01 and HPST99-INT01)

The number of subjects/patients exposed and the duration of exposure to Helicide during clinical development is shown in Table 1 below:

TABLE 1
Extent of Exposure in Helicide Clinical Trials
Number of Subjects/Patients per Treatment

Trial		Duration of Treatment	Number of Subjects/Patients		Total
			Helicide	Control	
Clin Pharm	HLD-PO-241	3 doses	23		23
	HLD-PO-180	6 days	36		36
Phase III	HPST99-CUS01	10 days	147	152	299
	HPST99-INT01	10 days	177		177
TOTALS			383	152	535

Other supportive clinical data includes:

- Two pilot studies using biscalcitrates, metronidazole, and tetracycline (with or without omeprazole) dispensed as separate formulations in a blister pack.

- Four clinical studies sponsored by independent investigators and conducted using a prototype single triple capsule with a slightly different drug content than Helicide. The capsule was administered with or without a proton pump inhibitor and for a varying duration of therapy. In these studies the applicant's role was limited to supplying study drug to the investigators.
- The FDA's findings of safety and effectiveness from the NDA 50-719 (Helidac® therapy, referenced under Section 505(b)(2) of the FD&C Act. Helidac® therapy (bismuth subsalicylate, metronidazole, and tetracycline) was approved by the FDA in 1996 in combination with an H₂-receptor antagonist for the treatment of patients with an active duodenal ulcer associated with *Helicobacter pylori* infection.
- Literature review of the efficacy of OBMT therapy, also referenced under Section 505(b)(2) of the FD&C Act

Clinical Reviewer's Comment: For combination therapy, it is important to document the contribution of each component to the overall efficacy of the regimen. Helidac therapy is comprised of three antimicrobial agents and is indicated for use in combination with the proton pump inhibitor (PPI) omeprazole. Literature data not submitted by the applicant was reviewed to provide supportive evidence of the contribution of each component to the efficacy of the treatment regimen.

B. Efficacy

The applicant conducted two Phase III trials. One trial was conducted in the US and Canada (Protocol HPST99-CUS01). The other Phase III trial is an international trial conducted in Europe, Australia, Canada and the US (Protocol HPST99-INT01).

In the North American trial, patients were randomized to Helicide plus omeprazole (OBMT) or a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC) and enrolled with a history of or current duodenal ulcer. The International trial differed from the North American trial in that all patients received OBMT. There was no comparator arm in the International trial. Also, the population enrolled in the International trial was symptomatic patients with gastrointestinal complaints (i.e., patients with non-ulcer dyspepsia). It was not necessary for these patients to have a history or current duodenal ulcer. The main efficacy endpoint for both trials is the absence (eradication) of *H. pylori* after treatment. Eradication is defined, according to guidelines, as two negative ¹³C urea breath tests (UBTs) done at least 4 and 8 weeks after the end of treatment.

Due to differences in the patient population enrolled in the two trials and the lack of a comparator arm in the International trial, the North American trial is considered pivotal and the International trial is considered supportive. The efficacy data from the International trial will not be discussed here, but can be found in the Integrated Summary of Efficacy (ISE).

1. North American Trial (Protocol HPST99-CUS01)

The *H. pylori* eradication rates at 8 weeks post-treatment (i.e., Day 56), are displayed for the applicant's Modified Intention-to-Treat (MITT) and Per Protocol (PP) analyses in Table 2. The reviewers are in agreement with the applicant's results.

Clinical and Statistical Reviewers' Comment: One patient in the OAC group was excluded from the PP population by the applicant due to an adverse event related to study

medication. The reviewers have included this patient in the population as a failure. The table below has been modified to reflect this change.

TABLE 2
***H. pylori* Eradication at Day 56 Visit**
Per Protocol and Modified Intention-to-Treat Analyses
(HPST99-CUS01)

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/125 (86.4) [80.4, 92.4]	6.1 [-1.5, 13.7]
Modified Intention-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

The applicant has followed the FDA draft Guidance for Industry – “Reduction of Gastric or Duodenal Ulcer Recurrence by Eradication of *H. pylori*” in determining efficacy of OBMT. According to the document, the following recommendations are made regarding establishment of an efficacy threshold.

Active controlled studies are strongly recommended and should be powered for statistical equivalence or superiority. The investigational regimen will be considered similar to the approved comparator if the lower bound of the 95% two-sided confidence interval for the difference in eradication rates (investigational regimen minus approved active therapy) lies above –15%.

The sponsor should discuss the choice of comparator regimens well in advance of beginning the study since it is recognized that some FDA approved regimens may be less ideal for comparative trials.

The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -2.1% for the MITT and PP analyses, respectively. Although the delta was not specified in the study protocol, the confidence intervals are within the recommended range of $\pm 15\%$ and the difference in the *H. pylori* eradication rate between the OBMT and the OAC treatment group (i.e., delta) satisfies the efficacy criteria recommended in the FDA draft Guidance.

2. Comparison With Other FDA-approved Regimens

Other FDA-approved treatment regimens indicated for *H. pylori* eradication in patients with an active or a history of duodenal ulcer are as follows:

Primary Therapy

- Omeprazole 40 mg QD + Clarithromycin 500 mg TID x 2 weeks. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of Omeprazole 20 mg QD is recommended for ulcer healing and symptom relief.
- Bismuth Subsalicylate 151 mg QID + Metronidazole 500 mg BID + Tetracycline 500 mg QID + an H₂-receptor antagonist (at treatment doses for an active duodenal ulcer) x 4 weeks

- Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 gram BID x 2 weeks
- Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 gram BID x 10 days
- Omeprazole 20 mg BID + Clarithromycin 500 mg TID + Amoxicillin 1 gram BID x 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of Omeprazole 20 mg QD is recommended for ulcer healing and symptom relief.
- Esomeprazole 40 mg QD + Clarithromycin 500 mg BID + Amoxicillin 1 gm BID x 10 days

Alternative Therapy*

- Lansoprazole 30 mg TID + Amoxicillin 1 gram TID x 2 weeks

*For those patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.

As seen in Table 3 below, the Per Protocol eradication rates achieved at 8 weeks post-treatment with Helicide plus omeprazole therapy (OBMT) in this submission appear comparable to those observed with other approved therapies. In addition, the eradication rate achieved with OAC in the North American trial (87.1% by Per-protocol analysis) is consistent with what has been reported previously.

**Appears This Way
On Original**

TABLE 3
FDA-Approved *H. pylori* Treatment Regimens

Antimicrobial Regimens	Dosage	Duration of Therapy	Eradication Rates Per-protocol Analysis#
Bismuth subsalicylate Metronidazole Tetracycline H ₂ -blocker*	2 chewable tablets (525 mg) QID 250 mg QID 500 mg QID ulcer-treatment doses	14 days 14 days 14 days 28 days	77%, 82%, 71% [‡]
Clarithromycin (Biaxin) Omeprazole (Prilosec)	500 mg TID 40 mg QD, then 20 mg QD [‡]	14 days 14 days 14 days (beginning on Day 15)	64%, 74%
Clarithromycin (Biaxin) Amoxicillin Lansoprazole (Prevacid)	500 mg BID 1 gm BID 30 mg BID	10 days 10 days 10 days	84%
Clarithromycin (Biaxin) Amoxicillin Lansoprazole (Prevacid)	500 mg BID 1 gm BID 30 mg BID	14 days 14 days 14 days	86%, 92%
Amoxicillin [†] Lansoprazole (Prevacid)	1 gm TID 30 mg TID	14 days 14 days	66%, 77%
Clarithromycin (Biaxin) Amoxicillin Omeprazole (Prilosec)	500 mg BID 1 gm BID 20 mg BID, then 20 mg QD [‡]	10 days 10 days 10 days 18 days (beginning on Day 11)	78%, 84%, 90%
Clarithromycin (Biaxin) Amoxicillin Esomeprazole (Nexium)	500 mg BID 1 gm BID 40 mg QD	10 days 10 days 10 days	84%, 85%

Evaluable patients were defined as having confirmed active or history of (within 2 years) duodenal ulcer disease and *H. pylori* infection at baseline and for whom results were available for the 4-6 week post-treatment visit

* Not included in Helidac[®] (bismuth subsalicylate, metronidazole, and tetracycline tablets/capsules packaged together)

[‡] In patients with a history of duodenal ulcer disease

[†] For patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected

[‡] In patients with an ulcer present at the time of initiation of therapy

C. Safety

The safety database for this NDA contains data on 383 subjects/patients exposed to Helicide plus omeprazole therapy (OBMT) from two clinical pharmacology studies, one pivotal Phase III trial (North American) and one supportive Phase III trial (International).

Due to differences in the patient population in two Phase III trials and the timing of assessments, the safety results for these two trials will not be pooled. The safety data from the International trial and the two clinical pharmacology studies will not be discussed here, but can be found in the Integrated Summary of Safety (ISS).

1. North American Trial (Protocol HPST99-CUS01)

Two hundred and ninety-nine (299) patients (147 in the OBMT group and 152 in the OAC group) were exposed to at least one dose of the study drugs and constitute the safety population in this study. Of these patients, 86/147 (58.5%) in the OBMT group and 90/152 (59.2%) in the OAC group report treatment emergent adverse events (TEAEs). TEAEs are defined as any event not present prior to exposure to study medication or any event already present that worsens in either intensity or frequency following exposure to study medication. In the OBMT group there are 212 events reported and 236 events reported in the OAC group.

Among these events, most are classified as mild to moderate intensity. Only four events are classified as severe in intensity in each group. Two adverse events are classified as serious, one death and one hospitalization; neither was deemed to be associated with study drug.

In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any TEAE. For both treatments gastrointestinal AEs are the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of metronidazole and/or tetracycline. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality is a common side effect and was more common in the OBMT group than the OAC group (15.6% versus 4.6%). The applicant noted that "stool abnormality" may refer to the darkening effect of bismuth on the stool and that it may have also been under-reported, since the patients were told *a priori* about this effect. Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Possible signs and symptoms of bismuth encephalopathy (e.g., myoclonic jerks, trembling, memory disturbances, confusion and problems of physical coordination) reported in the OBMT group are: asthenia in 6 patients (4.1%) and amnesia in one patient. Asthenia is also reported in the OAC group in 4 patients (2.6%). Based on these events, it is unlikely that 10 days of treatment with Helicide causes bismuth-associated encephalopathy.

There are no clinically meaningful changes from pre-study to the end of the study visit within or between treatment groups in any of the laboratory parameters analyzed. Patients in both treatment groups experience increases in ALT and AST levels. When individual patient data are reviewed, however, only three patients are considered to have clinical significant findings by the investigators in the OBMT group while no patient is considered to have a clinically significant finding in the OAC group. The clinical relevance of these changes is not known.

There were no clinically relevant changes observed in physical exam findings or vital signs.

D. Dosing

The proposed regimen for Helicide therapy is three Helicide capsules administered four times daily after meals and at bedtime given with omeprazole 20 mg twice daily after breakfast and supper for 10 days. The dose of each component contained in one Helicide capsule and the total daily doses are shown below in Table 4.

TABLE 4
Composition of Helicide Capsule and Total Daily Dose of BMT Therapy

	Dose per capsule	Total Daily Dose (12 capsules/day)
Bismuth subcitrate	140 mg (40 mg as Bi ₂ O ₃ equivalent)	1680 mg (480 mg as Bi ₂ O ₃ equivalent)
Metronidazole	125 mg	1500 mg (1.5 gm)
Tetracycline HCl	125 mg	1500 mg (1.5 gm)

Although the applicant did not conduct formal dose ranging studies, efficacy data were obtained from two pilot studies, which helped to refine the dosing and duration of treatment. The results from these studies indicate that 1.0 gram of tetracycline per day is insufficient and 14 days of treatment is better than 7 days. A 10-day treatment regimen is proposed for approval and is the duration of therapy selected for study in the Phase III trials based on the approved duration of therapy for the active control arm (OAC therapy). Published treatment guidelines in the United States also recommend at least 10 days of therapy in order to achieve acceptable eradication rates. The proposed daily dose of metronidazole is higher than the 1.0 gram per day used in the pilot studies. The applicant believes the higher dose is more efficacious in the presence of metronidazole-resistant bacterial strains and is still within the range of doses used in similar regimens in the literature.

The applicant originally proposed administering the Helicide treatment regimen on an empty stomach (i.e., before meals) in the Phase III trials, as was done in the two pilot studies. The Division questioned the applicant as to the rationale for dosing on an empty stomach, since medications in the FDA-approved Helidac® regimen (bismuth subsalicylate, metronidazole, and tetracycline) are indicated to be taken with meals. It has also been shown that administration of ranitidine bismuth citrate (Tritec®) with food increases eradication rates compared to administration on an empty stomach (Webb, et al. Am J Gastroenterol 1995;90:1273-7). In response, the applicant modified the dosing of Helicide in the Phase III trials to after meals. The rationale is that a prolonged gastric residence time of the capsule, induced by the fed state, increases the duration of contact between the bacteria and the active drug leading to improved eradication rates.

E. Special Populations

Patients with renal or hepatic impairment, pediatric patients, and pregnant women were excluded from the Helicide development program. Metronidazole is metabolized by the liver to a great extent and should be avoided in patients with hepatic impairment. Tetracycline hydrochloride is labeled as Pregnancy Category D due to retardation of skeletal development and embryotoxicity. Therefore, Helicide will be labeled as contraindicated in

pregnant (Pregnancy Category D) or nursing women, pediatric patients (under the age of 12 years), and in patients with renal or hepatic impairment.

1. Efficacy

Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories were performed by the reviewers to determine whether any of these covariates had a significant effect on *H. pylori* eradication rates. The results indicate that none of these covariates have a statistically or clinically significant effect on eradication status, based on the reviewers' assessment.

2. Safety

The results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also have a higher incidence of nausea and taste perversion. Overall, these differences are slight and unlikely to result in clinically meaningful differences.

The numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly and between the various racial subgroups.

**Appears This Way
On Original**

CLINICAL/STATISTICAL REVIEW

I. Introduction/Background

A. Overview of Drug, Dosage, and Indications

Drug

Generic Name:	Biscalcitrates potassium + Metronidazole + Tetracycline HCl
Pharmacologic Category:	Mucosal Protectant (Biscalcitrates potassium) and Antimicrobial (Metronidazole and Tetracycline)
Proposed Trade Name:	Helicide®
Molecular Formula:	Biscalcitrates potassium (BiC ₁₂ H ₁₀ K ₅ O ₁₅) ₆ or (BiC ₁₂ H ₁₀ K ₅ O ₁₅) ₆ .
Molecular Weight:	<u> </u> daltons
Dosage Form:	Capsule containing biscalcitrates 140 mg + metronidazole 125 mg + tetracycline 125 gm
Route of Administration:	Oral

Applicant's Proposed Indication

Helicide capsules (biscalcitrates potassium, metronidazole, and tetracycline hydrochloride), in combination with omeprazole are indicated for the eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease (active or by history). The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.

Applicant's Proposed Dosing and Administration

Helicide should be given as three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

B. Important Milestones in Product Development

The applicant initially submitted a Pre-IND on July 30, 1998. The applicant proposed a US trial of Helicide capsules plus a proton pump inhibitor (PPI) in duodenal ulcer patients. The US study was to be a pivotal Phase III trial and a Canadian trial in duodenal ulcer and non-ulcer dyspepsia patients would be supportive. In response to DSPIDPs comments, including the need for an active comparator arm and for using the same PPI in the US and Canada, the applicant revised the study protocols and submitted an IND on July 20, 1999. In the IND the pivotal trial was a single, joint US-Canadian study of Helidac with omeprazole in duodenal ulcer patients with an additional supportive trial in duodenal ulcer and non-ulcer dyspepsia patients in Europe, Australia, Canada and the US. The North American trial would use an active-control and the primary endpoint would be the difference in eradication rates between the two treatments. The applicant selected the FDA-approved treatment of omeprazole, amoxicillin, and clarithromycin (OAC) as the active-control. OAC was considered acceptable by DSPIDP as it consistently achieves eradication rates of approximately 70% or greater by Modified Intention-to-Treat (MITT) analysis and 80% or greater by Per Protocol (PP) analysis. It was agreed that the International study would be non-comparative.

A pre-NDA meeting was held on January 11, 2001. At this meeting it was agreed that the applicant could file an NDA for approval of Helicide using FD&C Act Section 505 (b) (2).

The applicant would cite the FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy) to support their application. It was also agreed the applicant would only present one adequate and well-controlled clinical trial in their application.

C. Other Relevant Information

At the current time, Helicide capsules are not registered in any other country. A New Drug Submission for Helicide capsules was sent to the Therapeutic Product Directorate in Canada on September 28, 2001 and is currently undergoing review.

II. Summary of Clinically Relevant Findings from Other Review Disciplines

A. Chemistry

The Office of Compliance is recommending non-approval of this product due to a failed Prior Approval Inspection (PAI) for the biscalcitrates component.

There are serious GMP concerns surrounding this application and _____ the manufacturer of the biscalcitrates drug substance. Under 21 CFR 314.125(b)(1), these deficiencies must be satisfactorily resolved prior to approval.

See complete review by Gene Holbert, Ph.D., Chemistry Reviewer in HFD-590 (DSPIDP) filed with this NDA (50-786).

B. Pharmacology/Toxicology

The application is approvable from the perspective of non-clinical pharmacology and toxicology.

The applicant did not conduct non-clinical studies in support of this NDA submission. Metronidazole and tetracycline are approved drug products. The proposed daily dose levels of 1,500 mg metronidazole and 1,500 mg tetracycline are approved therapeutic doses. The dosing duration of 10 days is within the approved dosing duration for each of these drugs. Therefore, non-clinical studies are not necessary for metronidazole and tetracycline.

Biscalcitrates potassium is similar to colloidal bismuth subcitrate (CBS), also referred to as tripotassium dicitrate bismuthate (Bi_2O_3), which is the active ingredient in De-Nolab, an approved drug product in Europe. Current accepted therapeutic daily doses of CBS in Europe deliver approximately 480 mg equivalents of Bi_2O_3 daily for up to 8 weeks. The proposed daily biscalcitrates potassium dose level expressed as mg equivalents of Bi_2O_3 is approximately 480 mg (i.e., 40 mg equivalents \times 3 tablets \times 4 daily doses). Any potential human toxicity from biscalcitrates potassium would be from excessive systemic concentrations of bismuth, particularly in the brain and central nervous system. There are, however, no indications of bismuth toxicity resulting from CBS therapy at the proposed dose.

A synopsis of pre-clinical animal toxicology data supplied by the applicant indicates that no adverse effects are observed in rats and dogs at each daily oral dose level of biscalcitrates potassium used in six month toxicity studies. The highest dose levels (converted to mg equivalents of Bi_2O_3) are 30 mg/kg and 18 mg/kg for rats and dogs, respectively. These

dose levels corresponded to human equivalent doses (based upon relative body surface area) of 4.8 mg/kg and 10 mg/kg (rat and dog studies, respectively). The approximate mg equivalents of Bi_2O_3 per kg body weight for the human dosing regimen is 7 mg/kg (for a 67 kg subject). Also cited are embryo-fetal development studies in rats and rabbits. No maternal and embryo-fetal effects are reported at any of the dose levels examined with the highest dose level in both rats and rabbits being 30 mg equivalents of Bi_2O_3 per kg body weight.

Biscalcitrates potassium can also be directly compared to bismuth subsalicylate (BSS), which is approved for over the counter use in the US as Pepto-Bismol®. The maximum recommended dose for BSS is approximately 4 grams per day, which corresponds to 2.3 grams of bismuth. This level of bismuth is almost 5-fold greater than the mg equivalents of Bi_2O_3 contained in the proposed daily oral dose of biscalcitrates potassium in the Helicide capsules.

In summary, there are no relevant non-clinical safety issues with the clinical use of Helicide for the eradication of *H. pylori*.

See complete review by Steven Hundley, Ph.D., Pharmacology/Toxicology Reviewer in HFD-590 (DSPIDP) filed with this NDA (50-786).

C. Clinical Pharmacology/Biopharmaceutics

The application is approvable from the clinical pharmacology and biopharmaceutics perspective.

The individual pharmacokinetics of bismuth salts, metronidazole, and tetracycline have all been previously reported in the scientific literature. The applicant was requested by the Division to perform three clinical pharmacology studies with Helicide:

1. a comparison of the bioavailability following a single clinical dose of biscalcitrates potassium, plus metronidazole, plus tetracycline hydrochloride formulated as Helicide capsules versus the three drugs given as separate tablets/capsules
2. a food effect study
3. a drug interaction study to compare the bioavailability of bismuth following multiple dose administration of Helicide capsules administered with and without omeprazole.

The results of the bioavailability study comparing administration of biscalcitrates potassium, metronidazole, and tetracycline hydrochloride formulated as Helicide capsules compared to administration as separate tablets/capsules containing the individual drug product demonstrate low and variable plasma concentrations of tetracycline and bismuth following administration of Helicide capsules compared to the individual tablets/capsules.

The results of the food effect study demonstrate decreased systemic exposure of bismuth, metronidazole, and tetracycline when administered as Helicide capsules with food as compared to fasting.

Despite lower exposure to one or more of the components of the Helicide capsule when administered in the Helicide dosage form or with food, clinical response (i.e., bacterial eradication) was achieved with the Helicide regimen in the clinical development program.

See complete review by Peter A. Dionne, Microbiologist in HFD-590 (DSPIDP) filed with this NDA (50-786).

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The individual pharmacokinetics of bismuth salts, metronidazole, and tetracycline are all well characterized in the scientific literature and will not be discussed here.

B. Pharmacodynamics

Although the applicant did not conduct formal dose ranging studies, efficacy data were obtained from pilot studies using various doses and duration of treatment with bismuth salts, metronidazole, and tetracycline (BMT) triple therapy alone and in combination with a proton pump inhibitor (PPI).

In the applicant's initial pilot study (HP93-C01), 57 patients received a treatment with bismuth salts 120 mg (equivalent to 40 mg Bi_2O_3) + metronidazole 250 mg + tetracycline 500

mg administered four times daily one hour before meals and at bedtime for 14 days. The Helicide capsules was not used. All three drugs were dispensed as separate formulations, packaged together in a blister pack. A control group of 35 patients received matching placebos. Eradication rates in the BMT arm in patients with or without duodenal ulcer(s) or history of duodenal ulcer were 81.5% in the Modified Intention-to-Treat (MITT) analysis and 89.8% in the Per Protocol (PP) analysis.

In an effort to increase efficacy, a second trial (HP97-C01) was undertaken with the addition of a proton pump inhibitor (omeprazole) to the BMT regimen. For patient convenience, the treatment duration was reduced from 14 days to 7 days and the tetracycline dose was reduced from 500 mg to 250 mg four times daily (i.e., 2 grams to 1 gram total daily dose). The dosing regimen in this study was bismaltrate 120 mg (equivalent to 40 mg Bi₂O₃) + metronidazole 250 mg + tetracycline 250 mg QID one hour before meals and at bedtime given with one omeprazole 20 mg tablet 1 hour before the morning and evening meal. As in the first pilot study, the three drugs were dispensed as separate formulations, packaged together in a blister pack. One hundred and sixty-one (161) patients with or without duodenal ulcer or history of duodenal ulcer were evaluable by MITT analysis and 146 by PP analysis. Eradication rates (95% Confidence Interval) were 80% (73.3%-85.7%) and 84% (78.3%-90.2%) for MITT and PP analysis, respectively.

The applicant concluded from these initial two studies that reducing the study duration from 14 days to 7 days and the daily dose of tetracycline from 2.0 grams to 1.0 gram/day was detrimental despite the addition of a PPI. This led to the final doses used in the Phase III trials and the proposed treatment regimen: bismaltrate (equivalent to Bi₂O₃ 120 mg) + metronidazole 375 mg + tetracycline 375 mg four times daily after meals and at bedtime given with omeprazole 20 mg twice daily after breakfast and supper for 10 days. A 10 day treatment regimen was selected for the Phase III trials since this is the duration of therapy for the FDA-approved active control regimen (OAC) and is in agreement with published recommendations regarding duration of treatment. The tetracycline dosage (1.5 grams/day) is higher than in the 7-day study (1.0 gram/day) since the eradication rate fell when this dose was used as compared to the 2.0 gram/day dose in the initial 14-day study. The tetracycline dose in the proposed regimen is limited at 1.5 grams/day by the size of the tetracycline capsule within the Helicide formulation. The metronidazole dose is increased to 1.5 grams/day from 1.0 gram/day used in the pilot studies. This dose is still within the range of doses used in similar regimens and reported in the literature. The applicant believes the higher dose is necessary to maintain efficacy in the presence of bacterial isolates with metronidazole resistance.

The applicant originally proposed administering the Helicide treatment regimen in the Phase III trials on an empty stomach (i.e., before meals) as was done in studies HP93-C01 and HP97-C01. The Division questioned the applicant as to the rationale for dosing on an empty stomach, since medications in the Helidac® regimen are indicated to be taken with meals. In addition, it has been shown that administration of ranitidine bismuth citrate (Tritec®) with food increases eradication rates compared to administration on an empty stomach (Webb, et al. Am J Gastroenterol 1995;90:1273-7). In response, the applicant modified the dosing to after meals based on the rationale that a prolonged gastric residence time of the drug, induced by the fed state, increases the duration of contact between *H. pylori* and the active medication leading to improved eradication rates. (Also, see Section VIII on Dosing, Regimen and Administration Issues).

IV. Description of Clinical Data and Sources

A. Overall Data

The worldwide clinical development program for Helicide in combination with omeprazole for the eradication of *H. pylori* includes:

- two Phase I (drug-drug interaction) studies
- two Phase III studies (HPST99-CUS01 and HPST99-INT01)

Other supportive clinical data includes:

- Two clinical trials using biscalcitrates, metronidazole, and tetracycline (with or without omeprazole) dispensed as separate formulations in a blister pack.
- Four pilot clinical studies conducted using a prototype single triple capsule with a slightly different drug content than Helicide. The capsule was administered with or without a proton pump inhibitor and for a varying duration of therapy. These studies were sponsored by independent investigators and the applicant's role was limited to supplying study drug.
- The FDA's findings of safety and effectiveness from the NDA 50-719 (Helidac® therapy, referenced under Section 505(b)(2) of the FD&C Act. Helidac® therapy (bismuth subsalicylate, metronidazole, and tetracycline) was approved by the FDA in 1996 in combination with an H₂-receptor antagonist for the treatment of patients with an active duodenal ulcer associated with *Helicobacter pylori* infection.
- Literature review of the efficacy of OBMT therapy, also referenced under Section 505(b)(2) of the FD&C Act

B. Table of Clinical Trials

The applicant conducted two Phase III trials. One trial was conducted in the US and Canada (Protocol HPST99-CUS01). The other Phase III trial was an international trial conducted in Europe, Australia, Canada and the US (Protocol HPST99-INT01). See Table 5 below for number of patients enrolled in the safety population for each trial.

In the North American trial, patients were randomized to Helicide plus omeprazole (OBMT) or a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC) and enrolled with a history of or current duodenal ulcer. The International trial differed from the North American trial in that all patients received OBMT. There was no comparator arm in the International trial. Also, the population enrolled in the International trial is symptomatic patients with gastrointestinal complaints (i.e., patients with non-ulcer dyspepsia). It was not necessary for these patients to have a history or current duodenal ulcer. The main efficacy endpoint for both trials is the absence (eradication) of *H. pylori* after treatment. Eradication is defined, according to guidelines, as two negative ¹³C urea breath tests (UBTs) done at least 4 and 8 weeks after the end of treatment.

TABLE 5
Helicide Phase III Clinical Trials

Trial	Location	Duration of Treatment	Number of Patients (Safety Population)		Total
			Helicide	Control	
HPST99-CUS01	US and Canada	10 days	147	152	299
HPST99-INT01	Europe, Australia, Canada, and US	10 days	177	--	177
TOTALS			383	152	535

V. Clinical Review Methods

A. Structure of the Review

For the purpose of obtaining the indication of *H. pylori* eradication, one North American Phase III trial (HPST99-CUS01) is considered pivotal. The International Phase III trial (HPST99-INT01) is considered supportive. This decision is based on the fact that there are differences in the patient population enrolled in the two trials (ulcer disease versus non-ulcer dyspepsia) and the International trial lacks a comparator arm.

B. Overview of Materials Consulted in Review

Material Submitted: 67 Volumes
Electronic data, including SAS transport files
\\CDSESUB1\N50786\N 000\2001-09-28
\\CDSESUB1\N50786\N 000\2001-12-19

Material Reviewed: Volume 1 and Volumes 31 through 42, 64 and 67
Electronic data, including SAS transport files
\\CDSESUB1\N50786\N 000\2001-09-28
\\CDSESUB1\N50786\N 000\2001-12-19

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested for this trial.

Clinical Reviewer's Comment: A routine DSI audit was not felt to be necessary for this NDA since metronidazole and tetracycline are not NMEs and bismuth (subsalicylate), metronidazole, and tetracycline have been used in combination for the same indication in another NDA application (Helidac NDA 50-719). All three compounds have well-characterized safety profiles. In addition, no discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.

D. Evaluation of Financial Disclosure

Financial disclosure information was obtained from each investigator. None of the investigators in the North American trial reported any significant equity interest.

**Appears This Way
On Original**

VI. Integrated Summary of Efficacy (ISE)

A. Brief Statement of Efficacy Conclusions

The applicant conducted one pivotal trial in North America (HPST99-CUS01) which documents the efficacy of Helicide therapy plus omeprazole (OBMT) compared to an FDA-approved active control regimen of omeprazole, amoxicillin and clarithromycin (OAC).

The results of the supportive data provide further evidence of the efficacy of OBMT therapy in eradication of *H. pylori*.

B. General Approach to Efficacy Review

Only the pivotal North American Phase III trial (HPST99-CUS01) was reviewed in detail. A synopsis is provide below and the complete clinical/statistical review can be found in Appendix 3. The International trial was not reviewed in detail, due to differences in the patient population compared to the North American trail and lack of a comparator arm, but is also summarized below.

Other supportive efficacy data summarized in this section includes:

- Pilot studies (2)
- Investigator sponsored studied (4)
- The FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy) [referenced under Section 505(b)(2) of the FD&C Act]
- Literature review of the efficacy of OBMT therapy, also referenced under Section 505(b)(2) of the FD&C Act

Clinical Reviewer's Comment: For combination therapy, it is important to document the contribution of each component to the overall efficacy of the regimen. Helidac therapy is comprised of three antimicrobial agents and is indicated for use in combination with a proton pump inhibitor (PPI), omeprazole. Literature data not submitted by the applicant was reviewed to provide supportive evidence of the contribution of each component to the efficacy of the treatment regimen.

- Literature review of the efficacy of OBMT therapy

Note: Tables in the ISE have been creased by the reviewers, unless otherwise noted.

C. Synopsis of Phase III Efficacy Results

1. North American Trial (HPST99-CUS01)

Title

Efficacy and Safety of Quadruple Therapy by Single-Triple Capsules of Biscalcitrates, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *H. pylori*: A Comparison to Omeprazole + Amoxicillin + Clarithromycin (HPST99-CUS01)

blank page

NDA 50-786

Helicide

Date of Study Initiation:
(First Patient Randomized) Sept 17, 1999

Date of Study Completion:
(Last Patient Visit) June 22, 2000

Date of Report: August 18, 2001

Published Abstracts: Gut 2000;47 Supp1:A100
Gastroenterol 2001;120(3)Supp1:A580

Study Sites

For this study 51 sites were recruited in the United States and Canada and 39 sites randomized at least one patient.

Objectives

The primary objective of this study is to determine the rate of *H. pylori* eradication following therapy with a single capsule (Helicide) containing bismaltrate, metronidazole, and tetracycline, given with omeprazole in *H. pylori* positive patients with current or history of duodenal ulcer(s).

Treatment

Patients were randomized to one of the following two treatment regimens for 10 days.

- Three (3) Helicide capsules four times daily, after meals and at bedtime plus one omeprazole 20 mg capsule twice a day after breakfast and supper (OBMT).
- One (1) clarithromycin 500 mg tablet + 2 amoxicillin 500 mg capsules plus one omeprazole 20 mg capsule twice a day before breakfast and supper (OAC).

Study Design

This is a multi-center, randomized, parallel group, open-label (investigator blinded) Phase III study of the efficacy and safety of 10-day therapy of Helicide capsules given with omeprazole (OBMT) compared to the FDA-approved regimen of omeprazole, amoxicillin and clarithromycin (OAC) in the eradication of *H. pylori*. A total of 299 patients received study therapy (147 OBMT and 152 OAC). The Modified Intention-to-Treat (MITT) population was comprised of 275 patients (138 OBMT and 137 OAC) and there were 244 patients in the Per Protocol (PP) population (120 OBMT and 124 OAC).

Pre-treatment biopsies of the gastric mucosa were taken to assess the presence of *H. pylori* and susceptibility to metronidazole and clarithromycin. A ¹³C-urea breath test (¹³C-UBT) and rapid urease test were also performed pre-treatment to confirm the presence of *H. pylori*. Eradication was confirmed by two negative UBTs at approximately four weeks (i.e., 28 days) and eight weeks (i.e., 56 days) after the end of study therapy. Patients presenting with a positive ¹³C-UBT at either time point underwent a second endoscopy with biopsies to reassess bacterial susceptibility post-treatment (i.e., emerging resistance) to metronidazole and clarithromycin.

Results

The mean age of the patients is 46.5 years in the OBMT group and 27.9 years in the OAC group. The majority of patients are male (59%), Caucasian (59%), and have a history of an ulcer (72%). Drug compliance (defined as $\geq 75\%$ of capsules taken, based on the number returned) is 89.8% and 93.4% for OBMT and OAC, respectively, in the safety population.

Overall Eradication

The *H. pylori* eradication rates at 8 weeks post-treatment (i.e., Day 56), are displayed for the applicant's Modified Intention-to-Treat (MITT) and Per Protocol (PP) analyses in Table 6. The reviewers are in agreement with the applicant's results.

Clinical and Statistical Reviewers' Comment: One patient in the OAC group was excluded from the PP population by the applicant due to an adverse event related to study medication. The reviewers have included this patient in the population as a failure. The table below has been modified to reflect this change.

TABLE 6
***H. pylori* Eradication at Day 56 Visit**
Per Protocol and Modified Intention-to-Treat Analyses
(HPST99-CUS01)

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/125 (86.4) [80.4, 92.4]	6.1 [-1.5, 13.7]
Modified Intention-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

The applicant has followed the FDA draft Guidance for Industry – “Reduction of Gastric or Duodenal Ulcer Recurrence by Eradication of *H. pylori*” in determining efficacy of OBMT. According to the document, the following recommendations are made regarding establishment of an efficacy threshold.

Active controlled studies are strongly recommended and should be powered for statistical equivalence or superiority. The investigational regimen will be considered similar to the approved comparator if the lower bound of the 95% two-sided confidence interval for the difference in eradication rates (investigational regimen minus approved active therapy) lies above -15%.

The sponsor should discuss the choice of comparator regimens well in advance of beginning the study since it is recognized that some FDA approved regimens may be less ideal for comparative trials.

The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -2.1% for the MITT and PP analyses, respectively. Although the delta was not specified in the study protocol, the confidence intervals are within the recommended range of $\pm 15\%$ and the difference in the *H. pylori* eradication rate between the OBMT and the OAC treatment group (i.e., delta) satisfies the efficacy criteria recommended in the FDA draft Guidance.

Eradication in Special Populations

Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories were performed by the reviewers to determine whether any of these covariates had a significant effect on *H. pylori* eradication rates. The results indicate that none of these covariates have a statistically or clinically significant effect on eradication status, based on the reviewers' assessment.

Eradication by Antimicrobial Susceptibility

Pre-treatment susceptibility to metronidazole and clarithromycin for the MITT and PP populations are shown in Tables 7 and 8 below.

TABLE 7
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
MITT Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	Susceptible	Resistant	Difference [95% CI]	Susceptible	Resistant	Difference [95% CI]
OBMT	68/74 (91.9)	41/51 (80.4)	-11.5 [-24.1, 1.0]	ND	ND	ND
OAC	ND	ND	ND	93/101 (92.1)	3/14 (21.4)	-70.7 [-92.8, -48.5]

ND = not done

Statistical Reviewer's Comments: The difference in eradication rates in the OBMT group between metronidazole susceptible and resistant isolates was calculated by the reviewer and found to be 11.5%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OBMT treated subjects, the rate of eradication in the resistant group is no more than 24.1% lower than that of the susceptible group.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates was calculated by the reviewer and found to be 70.7%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OAC treated subjects, the rate of eradication in the resistant group is at least 48.5% lower than that of the susceptible group.

TABLE 8
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
PP Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	Susceptible	Resistant	Difference [95% CI]	Susceptible	Resistant	Difference [95% CI]
OBMT	61/64 (95.3)	38/44 (86.4)	-8.9 [-20.3, 2.4]	ND	ND	ND
OAC	ND	ND	ND	88/93 (94.6)	3/13 (23.1)	-71.6 [-94.9, -48.2]

ND = not done

Statistical Reviewer's Comment: The difference in eradication rates in the OBMT group between metronidazole susceptible and resistant isolates was calculated by the reviewer and found to be 8.9%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OBMT treated subjects, the rate of eradication in the resistant group is no more than 20.3% lower than that of the susceptible group.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates calculated by the reviewer and was found to be 71.6%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OAC treated subjects, the rate of eradication in the resistant group is at least 48.2% lower than that of the susceptible group.

Eradication by Duration of Disease

Eradication rates for patients with active duodenal ulcers compared to those with a history of ulcer disease are shown in Tables 9 and 10 by treatment group for the MITT and PP analyses, respectively. Given the small number of patients in the groups with an active ulcer and with a history of duodenal ulcer > 2 years ago, statistical comparisons were not attempted by the applicant.

Clinical Reviewer's Comment: Tables 9 and 10 were adapted by the reviewer from the applicant's original tables.

TABLE 9
Eradication Rates (n/N) [95% CI] by Disease History
MITT Population (HPST99-CUS01)

Treatment	Active Duodenal Ulcer	History of Duodenal Ulcer	
		≤ 2 years ago	> 2 and ≤ 5 years ago
OBMT	100% (15 / 15)	85.1% (97 / 114) [78.5; 91.6]	100% (12 / 12)
OAC	92.3% (12 / 13) [77.8; 106.8]	82.8% (96 / 116) [75.9; 89.6]	75% (6 / 8) [45.0; 105]

TABLE 10
Eradication Rates (n/N) [95% CI] by Disease History
PP Population (HPST99-CUS01)

Treatment	Active Duodenal ulcer	History of Duodenal Ulcer	
		≤ 2 years ago	> 2 and ≤ 5 years ago
OBMT	100% (14 / 14)	90.7% (88/97) [84.9; 96.5]	100% (9/9)
OAC	91.7% (11 / 12) [76.0; 107.3]	87.5% (91/104) [81.1; 93.9]	75% (6/8) [45.0; 105]

Rates of Emerging Resistance

Changes in susceptibility to clarithromycin and metronidazole were assessed post-treatment in patients who failed eradication. Unfortunately, many patients refused to have a second endoscopy after treatment. Available results for metronidazole and clarithromycin are presented for the MITT population in Table 11 below.

Statistical Reviewer's Comment: Table 11 should be interpreted with caution as the small number of patients for which data are available most likely do not represent the entire original MITT population.

Clinical Reviewer's Comment: Table 11 was adapted from two of the applicant's tables by the reviewer.

TABLE 11
Baseline *H. pylori* Susceptibility Results vs. Eradication Status After Treatment
MITT Population (HPST99-CUS01)

Susceptibility to Metronidazole at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy			Susceptibility to Clarithromycin at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy		
		R	S	M			R	S	M
Resistant	10	5		5	Resistant	11			
Susceptible	6	1		5	Susceptible	8	1	1	6
Missing	1			1	Missing	4	1		3
Total	17				Total	23			

R = resistant; I = intermediate; S = susceptible; M = Missing

Metronidazole: R \geq 8 μ g/mL; S \leq 4 μ g/mL

Clarithromycin: R \geq 1 μ g/mL; I = 0.5 μ g/mL; S \leq 0.25 μ g/mL

Clinical Reviewer's Comment: The applicant defines metronidazole resistance as a MIC \geq 8 μ g/mL.

Instead, the same data can be represented using MIC values as shown in Table 12 below, which was created by the FDA reviewing microbiologist

TABLE 12
Metronidazole Susceptibility Test Results and
Clinical/Bacteriological Outcomes^a for HELICIDE Therapy
(Three HELICIDE® capsules four times a day
plus omeprazole 20 mg twice daily for 10 days)

Metronidazole Pretreatment Results	<i>H. pylori</i> negative (Eradicated)	<i>H. pylori</i> positive (Not Eradicated)		
		Post-treatment susceptibility results		
		MIC \leq 8	MIC \geq 16	No MIC
MIC \leq 8 μ g/mL 74	67	0	2	5
MIC \geq 16 μ g/mL 51	42	0	4	5

^a Includes only patients with pretreatment metronidazole susceptibility test results

Conclusions

The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -2.1% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are within the recommended range of \pm

15% and the *H. pylori* eradication rates for the OBMT treatment satisfies the efficacy criteria recommended in the FDA draft Eradication Guidance

2. International Trial - Protocol HPST99-INT01

Title

Efficacy and Safety of Quadruple Therapy by Single Triple Capsules of Bismuth Subcitrate, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *H. pylori*

Date of Study Initiation

(First Patient Enrolled): 03 March 2000

Date of Study Completion

(Last Patient Visit): 25 September 2000

Date of the report:

17 August 2001

Study Sites

This study was conducted in Australia, Europe, and North America. There were 8 study sites.

Objectives

The primary objective of this study was:

- To determine the rate of *H. pylori* eradication following therapy with a single capsule (Helicide) of bismuth subcitrate, metronidazole, and tetracycline, given with omeprazole, in *H. pylori* positive patients.

Treatment

Helicide 3 capsules four times daily, after meals and at bedtime, plus one omeprazole 20 mg capsules after breakfast and supper (OBMT) for 10 days.

Study Design

This is an open-label, non-comparative, multi-center, Phase III study of the efficacy and safety of 10-day therapy with Helicide capsules given with omeprazole (OBMT) in the eradication of *H. pylori*. A total of 177 patients received study therapy, and 159 patients completed the study. The Modified Intention-to-Treat (MITT) population was comprised of 170 patients, and there were 146 patients in the Per Protocol (PP) population.

Pre-treatment biopsies of the gastric mucosa were taken to assess the presence of *H. pylori* and susceptibility to metronidazole and clarithromycin. A ¹³C-urea breath test (¹³C-UBT) and rapid urease test were also performed pre-treatment to confirm the presence of *H. pylori*. Eradication was confirmed by two negative UBTs at approximately four weeks and eight weeks after the end of study therapy. Patients presenting with a positive ¹³C-UBT at either time point underwent a second endoscopy with biopsies to reassess bacterial susceptibility to metronidazole and clarithromycin.

Results

The mean age of the patients is 51 years. Approximately 60% of the patients were male, and the majority of the patients (> 88%) are Caucasian. Drug compliance (defined as ≥ 75% of medications taken) is 96.84% and 97.72% for the Helicide and omeprazole capsules,

respectively, in the MITT population and 98.56% and 99.45%, respectively, in the PP population, based on the number of returned capsules.

The overall eradication rates for OBMT in the PP and MITT analyses are shown in Table 13 below.

TABLE 13
Overall *H. pylori* Eradication at the Day 56 Visit
Per Protocol and Modified Intention-to-Treat Analyses
(HPST99-INT01)

	Per-Protocol n/N (%) [95% CI]	MITT n/N (%) [95% CI]
OBMT	142/146 (97.3) [94.6; 99.9]	158/170 (92.9) [89.1; 96.8]

Eradication rates for OBMT for organisms found to be susceptible or resistant to metronidazole before treatment are shown in Table 14 below.

*Clinical Reviewer's Comment: The applicant defined metronidazole resistance as a MIC \geq 8 μ g/mL. However, the NCCLS has not defined metronidazole breakpoints for *H. pylori*, therefore, the word resistant should not be used. Instead, the data can be represented using MIC values as shown in Table 14 below.*

TABLE 14
Eradication Rates (%) by Pre-Treatment Metronidazole Susceptibility
Per Protocol and Modified Intention-to-Treat Analyses
(HPST99-INT01)

	Per-Protocol n/N (%)	ITT n/N (%)
Metronidazole MIC \leq 4 μ g/mL	75/76 (98.7)	82/86 (95.3)
Metronidazole MIC \geq 8 μ g/mL	38/40 (95.0)	40/43 (93.0)

Eradication rates for metronidazole strains with a MIC \leq 4 μ g/mL are not significantly different from those with a MIC \geq 8 μ g/mL for either the PP or MITT analyses, but are based on a relatively small sample size and may not represent the entire PP or MITT population.

There are 106/170 patients in the MITT population, and 89/146 patients in the PP population with either history or endoscopic confirmation of a duodenal or gastric ulcer or a history of non-ulcer dyspepsia. For the MITT population, eradication rates for patients in the duodenal ulcer, gastric ulcer, and non-ulcer dyspepsia categories are 90.7% (39/43), 100% (14/14), and 93.9% (46/49), respectively. Eradication rates in the PP population were similar or slightly higher, i.e., 94.4% (34/36), 100% (12/12), and 97.6% (40/41) for patients in the duodenal ulcer, gastric ulcer, and non-ulcer dyspepsia categories, respectively.

Statistical comparisons show no significant differences in the eradication rates between patients with history or endoscopic confirmation of peptic ulcer (duodenal or gastric ulcer) and history of non-ulcer dyspepsia for either analysis population.

Conclusions

Overall eradication rates for OBMT therapy in the International trial are consistent with, although numerically higher than, the results obtained in the OBMT arm in the North American study for the MITT (92.9% versus 87.7%) and PP (97.3% versus 92.5%) analyses, respectively. These results are similar to other drug therapy trials in which *H. pylori* eradication rates are often higher in European patients than those in North America.

D. Other Supportive Efficacy Data

1. Pilot Studies

In the applicant's initial study (HP93-C01), 57 patients received a treatment with bismaltrite 120 mg (equivalent to 40 mg Bi₂O₃) + metronidazole 250 mg + tetracycline 500 mg (BMT) administered four times daily one hour before meals and at bedtime for 14 days. The Helicide capsule was not used. All three drugs were dispensed as separate formulations, but packaged together in a blister pack. A control group of 35 patients received matching placebos. Eradication rates in the BMT arm in patients with or without duodenal ulcer(s) or history of duodenal ulcer were 81.5% in the Modified Intention-to-treat (MITT) and 89.8% in the Per Protocol (PP) analysis.

In an effort to increase efficacy, a second trial (HP97-C01) was undertaken with the addition of a proton pump inhibitor (omeprazole) to the BMT regimen. For patient convenience, the treatment duration was reduced from 14 days to 7 days and the tetracycline dose was reduced from 500 mg to 250 mg four times daily. The dose regimen in this study consisted of bismaltrite 120 mg (equivalent to 40 mg Bi₂O₃) + metronidazole 250 mg + tetracycline 250 mg administered four times daily one hour before meals and at bedtime given with one omeprazole 20 mg tablet one hour before the morning and evening meal. As in the first pilot study, the Helicide capsule was not used. All three drugs were dispensed as separate formulations, but packaged together in a blister pack. One hundred and sixty-one (161) patients with or without duodenal ulcer or history of duodenal ulcer were evaluable by MITT analysis and 146 in the PP analysis. Eradication rates (95% Confidence Interval) were 80% (73.3%-85.7%) and 84% (78.3%-90.2%) for MITT and PP analysis, respectively.

2. Investigator Sponsored Trials

Four studies were also carried out using a prototype to the Helicide capsule by independent investigators. The applicant supplied the study drug(s) to the investigators. The prototype capsule contained bismaltrite (equivalent to Bi₂O₃ 60 mg) + metronidazole 125 mg + tetracycline 125 mg and was administered as two capsules after meals and before bedtime. MITT eradication rates are shown in Table 15 below.

Reviewer's Comment: The Modified Intention-to-Treat (MITT) analyses reported in the table below were conducted by the applicant. It is possible that the authors performed their analyses on a slightly different database and therefore the results below may not match those in the published literature. The applicant has attempted to provide as accurate a summary as possible based on the data available to them at this time.

Table 15 below was adapted from the applicant's table.

TABLE 15
Summary Results of Investigator Sponsored Trials

BMT plus...	Number of patients	MITT eradication rate
Without PPI x 10 days ¹	53	50/53 (94.3%)
Lansoprazole 30 mg BID x 7 days ²	66	54/65 (83.1%)
Omeprazole x 7 days ³	65	56/65 (86%)
Pantoprazole 40 mg BID x 7 days ³	33	27/33 (81.8%)

¹de Boer WA, Van Etten RJXM, Schneeberger PM, et al. A single drug for *Helicobacter pylori* infection: First results with a new bismuth triple moncapsule. Am J Gastroenterol 2000;95:641-5.

²de Boer WA, Van Etten RJXM, Van De Wouw BAM, et al. Bismuth-based quadruple therapy for *Helicobacter pylori* – A single triple capsule plus lansoprazole. Aliment Pharmacol Ther 2000;14:85-9.

³unpublished

3. Helidac Therapy (NDA 50-719)

The FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy), referenced under Section 505(b)(2) of the FD&C Act, was considered to be supportive data for the Helicide NDA.

On August 15, 1996 Helidac therapy was approved in combination with an H₂-receptor antagonist for the treatment of patients with an active duodenal ulcer associated with *H. pylori* infection. The Helidac NDA was also a literature-based application under FD&C Act Section 505(b)(2).

Helidac therapy consists of bismuth subsalicylate 525 mg (two 262.4 mg chewable tablets), 250 mg metronidazole (one 250 mg tablet), and 500 mg tetracycline (one 500 mg capsule) taken four times daily (at meals and bedtime) for 14 days plus an H₂-receptor antagonist approved for the treatment of acute duodenal ulcer. The bismuth, metronidazole, and tetracycline capsules are packaged together in 14 blister cards, one for each day of therapy. The H₂-receptor antagonist is prescribed separately.

The Helidac clinical database consists of two randomized, controlled trials by Graham et al. (References 1 and 2 below) and Labenz et al (Reference 3) and one uncontrolled trial by Cutler et al (Reference 4). Based on audit results from the Division of Scientific Investigation, Dr. Graham study was considered valid. Audit of Dr. Labenz's study site was unable to be undertaken because of lack of agreement on the conditions of the inspection. As a result, the Labenz study was not validated and the Cutler study was used as the second pivotal trial.

1. Graham DY, Lew GM, Evans DG, et al. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. Ann Intern Med 1991;115:266-69.
2. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. Ann Intern Med 1992;116:705-8.

3. Labenz J, Gyenes E, Ruhl GH, et al. Amoxicillin plus omeprazole versus triple therapy for eradication of *Helicobacter pylori* in duodenal ulcer disease: A prospective randomized, and controlled study. *Gut* 1993;34:1167-70.
4. Cutler AF, Schubert TT. Long-term *Helicobacter pylori* recurrence after successful eradication with triple therapy. *Am J Gastroenterol* 1993;88:1359-61.

Eradication rates in patients with active duodenal ulcer disease following Helidac therapy plus an H₂-receptor antagonist are shown in Table 16 below and are taken from the Helidac package insert:

Clinical Reviewer's Comment: The table below was created by the reviewer and the formatting is not identical to the table found in the Helidac package insert (e.g., the footnote numbering has been changed).

TABLE 16
***H. pylori* Eradication Following Use of Helidac Therapy**

Investigator	Eradication Rate in Duodenal Ulcer Patients*	95% Confidence Intervals
Graham ^{1,2}	77% (N = 39)	61% - 89%
Cutler ⁴	82% (N = 51)	70% - 92%

*Evaluable patients were defined as having a confirmed duodenal ulcer within 2 years prior to treatment and having taken 14 days of bismuth subsalicylate, metronidazole, and tetracycline (range 11 to 17 days). Eradication was defined as no evidence of *H. pylori* infection by culture, rapid urease test and/or urea breath test from at least 4 weeks post-treatment up to 1 year post-treatment.

As seen in the table, the eradication rates in patients with active duodenal ulcers obtained with Helidac therapy plus an H₂-receptor antagonist are lower than those obtained in patients with active or a history of duodenal ulcer disease in the North American study with Helicide plus omeprazole (92.5% in the PP analysis and 87.7% in the MITT analysis).

Clinical Reviewer's Comments:

The Helidac® results were obtained using an evaluable population, which included patients with a confirmed duodenal ulcer and excluded dropouts and patients with missing H. pylori tests post-treatment. This population is not consistent with either the MITT or PP population, as defined in the DAIDP. Guidance for Industry - Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products. Indication 25: H. pylori (FDA, 1997: draft). Therefore, it is not labeled as such in the package insert.

All patients in the Helidac® studies had active ulcer disease, while patients in the Helicide studies were obtained from patients with active ulcers or a history of ulcer disease. The applicant has demonstrated in their submission that the eradication rates between the two populations are comparable.

4. Literature Review - Contribution of Each Drug to Efficacy

For combination therapy, it is important to document the contribution of each component to the overall efficacy of the regimen. Helidac therapy is comprised of three antimicrobial

agents and is indicated for use in combination with the proton pump inhibitor (PPI) omeprazole. Literature data was reviewed to provide supportive evidence of the contribution of each component to the efficacy of the OBMT treatment regimen.

Clinical Reviewer's Comment: The following data obtained from literature publications were not submitted as part of the applicant's NDA, but were obtained and included by the reviewer, as supportive data.

Bismuth, Metronidazole, and Tetracycline (BMT) Therapy

Bismuth salts exert local effects on the gastroduodenal mucosa, including cytoprotective and ulcer healing properties. In addition bismuth compounds kill *H. pylori* organisms by various mechanisms, including inhibition of protein and cell wall synthesis, membrane function, and ATP synthesis. Adherence of *H. pylori* to surface epithelial cells is also impaired. Bismuth monotherapy is effective at suppression of the organism, but clinical cure (i.e., eradication) rates are low. Addition of one to two antibiotics increases eradication rates.

In order to determine eradication rates for single versus dual versus triple antimicrobial therapy, a meta-analysis was performed by Chiba et al. Eradication rates were obtained from literature articles published between 1982 and 1990. The contribution of each antimicrobial to eradication can be seen in Table 17 below.

Chiba N, Rao BV, Rademaker JW, et al. Meta-analysis of the efficacy of antibiotic therapy in eradicating Helicobacter pylori. Am J Gastroenterol 1992;87:1716-27.

TABLE 17
Eradication Rates by Bismuth Treatment Regimen

Regimen	Number Eradicated / Number Treated	Eradication Rate (%)
Bismuth Alone	76 / 387	19.6 %
Bismuth + Metronidazole	65 / 118	55.1 %
Bismuth + Metronidazole + Tetracycline	191 / 203	94.1 %

BMT Plus Proton Pump Inhibitor (Omeprazole) Therapy

In the proposed Helicide regimen, bismuth triple therapy is combined with the proton pump inhibitor (PPI) omeprazole. Two published literature articles have attempted to address whether addition of a PPI improves eradication when added to bismuth triple therapy.

- *De Boer W, Driessen W, Jansz A, et al. Effect of acid suppression on efficacy of treatment for Helicobacter pylori infection. Lancet 1995;345:817-20.*

Patients with peptic ulcer disease and biopsy-proven *H. pylori* infection received triple therapy for 7 days (colloidal bismuth subcitrate 120 mg four times daily, metronidazole 500 mg three times daily, and tetracycline 500 mg four times daily). In addition, they were randomly assigned to treatment with omeprazole 20 mg twice daily for 10 days, beginning three days before triple therapy, or placebo. Eradication rates, as assessed by endoscopic methods, are shown in Table 18 below.

TABLE 18
BMT Eradication Rates with or without Addition of a PPI
(De Boer et al 1995)

OBMT n/N (%)	BMT n/N (%)	Difference % [95% CI]	p-value
53/54 (98.1%)	45/54 (83.3%)	14.8% [4.2; 25.4]	0.02

Clinical Reviewer's Comment: The regimens studied in this paper are slightly different than the proposed Helicide plus omeprazole regimen. The OBMT regimen used in this study employed 3 days of pre-treatment with omeprazole prior to initiating BMT therapy and the duration of O plus BMT therapy was only 7 days.

- Borody TJ, Andrews P, Fracchia G, et al. Omeprazole enhances efficacy of triple therapy in eradicating *Helicobacter pylori*. *Gut* 1995;37:477-81.

Symptomatic dyspeptic patients with biopsy-proven *H. pylori* infection received triple therapy five times a day for 12 days (colloidal bismuth subcitrate 108 mg, metronidazole 200 mg, and tetracycline 250 mg). In addition, they were randomized to either 20 mg of omeprazole twice a day or 40 mg of famotidine at bedtime. Eradication rates, as assessed by endoscopic methods, are shown in Table 19 below.

TABLE 19
BMT Eradication Rates with or without Addition of a PPI
(Borody et al 1995)

OBMT n/N (%)	BMT (plus famotidine) n/N (%) [95% CI]	Difference %	p-value
122/125 (97.6%)	110/124 (88.7%)	8.9%	0.006

Clinical Reviewer's Comment: The regimens studied in this paper are also slightly different than the proposed Helicide plus omeprazole regimen. The duration of BMT therapy was for 12 days and the BMT regimen also included famotidine. However, it is widely accepted that H₂-receptor antagonists, unlike PPIs, contribute little, if anything, to eradication.

In summary, the addition of each antimicrobial agent appears to contribute to the overall efficacy of the BMT regimen. Also, addition of a proton pump inhibitor (omeprazole) appears to increase the eradication rate achieved by BMT therapy.

5. Literature Review – Efficacy of OBMT Therapy

Clinical Reviewer's Comment: The following data were obtained from literature publications were submitted by the applicant as part of the NDA. Table 20 in Appendix 1 was also created by the applicant.

The applicant reviewed 31 literature articles in which OBMT therapy was used with various drug doses and duration of treatment. Table 20 in Appendix 1 summarizes these studies. When limited to studies evaluating a treatment duration of 7 days or more, the results show, by MITT analysis, 2281 patients out of 2654 are cured (85.9%). Breakdown by metronidazole susceptibility is reported for some of these studies. Two hundred and sixteen of 236 patients (91.5%) with metronidazole susceptible strains are cured (versus 91.9% in the North American trial). Also, 129/167 (75.9%) patients with metronidazole resistant strains are cured (versus 80.4% in the North American trial). The applicant also points out that there is a trend showing higher eradication rates with higher doses of metronidazole (1.5 to 2 grams per day versus 1 gram per day).

E. Summary of Efficacy

The applicant conducted one pivotal trial in North America (HPST99-CUS01) to document the efficacy of Helicide therapy plus omeprazole (OBMT). It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -2.1% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are within the recommended range of $\pm 15\%$ and the *H. pylori* eradication rates for the OBMT treatment satisfies the efficacy criteria recommended in the FDA draft Eradication Guidance.

Other findings include:

- Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories indicate that none of these covariates have a statistically or clinically significant effect on eradication status.
- The rate of eradication in the OBMT group in patients whose bacterial isolates pre-treatment are resistant to metronidazole (defined as an MIC $\geq 8 \mu\text{g/mL}$) is no more than 24.1% or 20.3% lower than in patients with a susceptible isolate pre-treatment in the MITT and PP analyses, respectively. Conversely, in the OAC group the rate of eradication in patients whose bacterial isolates pre-treatment are resistant to clarithromycin (defined as an MIC $\geq 1 \mu\text{g/mL}$) is at least 48.5% or 48.2% lower than that of the susceptible group in the MITT and PP analyses, respectively.
- No conclusions can be drawn regarding the rates of emerging resistance to either OBMT or OAC due to the few number of patients with culture results available post-treatment.

The results of the supportive data provide further evidence of the efficacy of Helicide therapy plus omeprazole (OBMT).

- The International trial (HPST99-INT01) demonstrates eradication rates (92.9% by MITT analysis and 97.3% by PP analysis) consistent with, and numerically greater than, the pivotal North American trial (87.7% by MITT analysis and 92.5% by PP analysis)
- Two pilot studies using BMT therapy administered as separate formulations in a blister pack with or without a PPI helped to refine the dosing regimen and treatment duration.

- Four investigator-sponsored trials of Helicide therapy using a prototype Helicide capsule with or without a PPI demonstrate eradication rates similar to what was observed in the Phase III trials.
- The FDA's findings of effectiveness from NDA 50-719 (Helidac® therapy) report eradication rates of 77-82%, which is lower than seen with Helicide plus omeprazole in the pivotal North American trial.
- Literature data demonstrates incremental increases in eradication rates achieved with each component of bismuth triple therapy over bismuth alone (19.6% for bismuth, 55.1% for bismuth plus metronidazole, and 94.1% for bismuth plus metronidazole plus tetracycline). Addition of a proton pump inhibitor (omeprazole) to BMT therapy also increases eradication rates (by 8.9 to 14.8%) over use of BMT alone.
- The efficacy of OBMT therapy in the literature (85.9% eradication by MITT analysis, when limited to studies using 7 days or more of therapy) is similar to the pivotal North American trial (87.7% by MITT analysis).

**Appears This Way
On Original**

VII. Integrated Summary of Safety (ISS)

A. Brief Statement of Safety Conclusions

There are no clinical meaningful differences between OBMT and OAC therapy in the incidence of adverse events (AEs) in the pivotal North American trial. Although the safety data from the International trial are not pooled with the North American trial, the results are supportive of each other with regards to OBMT therapy. The AEs reported for OBMT therapy in both trials do not suggest that patients experience neurotoxicity related to bismuth after exposure to Helicide therapy.

B. Description of Drug Exposure

The safety database for this NDA contains data from two clinical pharmacology studies, one pivotal Phase III trial and one supportive Phase III trial. The number of patients exposed and the duration of exposure is shown in Table 21 below.

The data from each of the four studies included in the database (i.e., two clinical pharmacology studies, one pivotal Phase III trial and one supportive Phase III trial) will be presented separately. Results will not be pooled.

Data from the initial two pilot clinical trials conducted by the applicant, which did not use the Helicide formulation (HP93-C01 and HP97-C01), as well as the four investigator sponsored trials, in which the applicant's role was to provide study drugs to the investigators, will not be discussed.

TABLE 21
Extent of Exposure in Helicide Clinical Trials
Number of Subjects/Patients per Treatment

Trial		Duration of Treatment	Number of Subjects/Patients		Total
			Helicide	Control	
Clin Pharm	HLD-PO-241	3 doses	23		23
	HLD-PO-180	6 days	36		36
Phase III	HPST99-CUS01	10 days	147	152	299
	HPST99-INT01	10 days	177		177
TOTALS			383	152	535

C. Methods and Specific Findings of Safety Review

The data from each of the four studies included in the database (i.e., two clinical pharmacology studies, one pivotal Phase III trial and one supportive Phase III trial) will be presented separately. Results will not be pooled.

In the safety review special attention was paid to the occurrence of any AE suggesting neurotoxicity. Elevated steady-state blood concentrations of bismuth are known induce a clinical syndrome of bismuth encephalopathy. Symptoms have an insidious onset. The patient first experiences weakness and fatigue followed by confusion, loss of memory, muscle twitching, loss of fine muscle control, and difficulty in walking. Ultimately, patients become bedridden, incontinent and disoriented.

Concentrations of > 50 ng/mL and > 100 ng/mL have been suggested in the literature as “safety” and “alarm” levels, respectively, for bismuth toxicity (see references below). Steady state concentrations of bismuth are reached after 4 to 5 weeks of chronic dosing. The recommended treatment duration of Helicide plus omeprazole therapy is 10 days, therefore, it is unlikely that patients receiving treatment will achieve steady state concentrations of bismuth or experience related toxicity.

Slikkerveer A and FA de Wolff. Pharmacokinetics and toxicity of bismuth compounds. Med Toxicol Adverse Drug Exp 1989; 4 (5): 303-323.

Serfontein WJ and al. Bismuth toxicity in man I. Bismuth blood and urine levels in patients after administration of a bismuth protein complex (Bicitropeptide). Res Comm Chem Pathol Pharmacol 1979; 26 (2): 383-389.

Serfontein WJ and R. Mekel. Bismuth toxicity in man II. Review of bismuth blood and urine levels in patients after administration of therapeutic bismuth formulations in relation to the problem of bismuth toxicity in man. Res Comm Chem Pathol Pharmacol 1979; 26 (2): 391-411.

Note: Tables in the ISS are obtained from the applicant’s submission, unless otherwise noted.

1. Overview of Adverse Events

North American Trial

In the pivotal trial, an adverse event (AE) was defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. A treatment emergent adverse event (TEAE) is defined as any event not present prior to exposure to study medication or any event already present that worsens in either intensity or frequency following exposure to study medication.

Two hundred and ninety-nine (299) patients (147 OBMT + 152 OAC) were exposed to at least one dose of the study drugs and constitute the safety population. Of these patients, 86/147 (58.5%) in the OBMT group and 90/152 (59.2%) in the OAC group reported TEAEs. In the OBMT group there are 212 events reported and 236 events reported in the OAC group. All TEAEs are shown in Table 22 in Appendix 3.

Among the TEAEs, most are classified as mild to moderate in intensity. Only four events are classified as severe in intensity in each group. They are headache, dyspepsia, apnea, and GI bleeding for OBMT and abdominal pain, taste perversion, vaginitis, and hematuria for OAC. The symptom of dyspepsia is rated as possibly related to study drug, taste perversion is rated as certainly related to study drug, and the others are rated as unlikely to be related to study drug.

Two adverse events are classified as serious TEAEs, one death and one hospitalization; neither is deemed to be associated with study drug. These patients are discussed further under the ISS Sections on Death and Non-Fatal Serious Adverse Events.

The most frequent TEAEs (incidence >1%) by treatment group are shown below in Table 23. For both treatments gastrointestinal adverse events are the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality is a relatively common side effect and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). The applicant noted that "stool abnormality" may refer to the darkening effect of bismuth on the stool and that it may have also been under-reported, since the patients were told *a priori* about this effect. Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Clinical Reviewer's Comment: Possible signs and symptoms of bismuth encephalopathy (e.g., myoclonic jerks, trembling, memory disturbances, confusion and problems of physical coordination) reported in the OBMT group are: asthenia in 6 patients (4.1%) and amnesia in one patient. Asthenia is also reported in the OAC group in 4 patients (2.6%). Based on these events, it is unlikely that 10 days of treatment with Helicide causes bismuth-associated encephalopathy.

**Appears This Way
On Original**

TABLE 23
Treatment-Emergent Adverse Events [n(%)] by Treatment Group
(Incidence > 1%, by Decreasing Frequency)
Study HPST99-CUS01

Preferred Term	OBMT (n = 147)	OAC (n = 152)
Stool Abnormality	23 (15.6)	7 (4.6)
Diarrhea	13 (8.8)	23 (15.1)
Dyspepsia	13 (8.8)	17 (11.2)
Abdominal Pain	13 (8.8)	15 (9.9)
Nausea	12 (8.2)	16 (10.5)
Headache	12 (8.2)	11 (7.2)
Flu Syndrome	8 (5.4)	5 (3.3)
Taste Perversion	7 (4.8)	18 (11.8)
Asthenia	6 (4.1)	4 (2.6)
Vaginitis	6 (4.1)	4 (2.6)
Dizziness	5 (3.4)	4 (2.6)
Lab Test Abnormality	4 (2.7)	4 (2.6)
Pain	3 (2.0)	7 (4.6)
Infection	3 (2.0)	5 (3.3)
Pharyngitis	3 (2.0)	4 (2.6)
Pain Back	3 (2.0)	2 (1.3)
SGPT Increased	3 (2.0)	0
Urinary abnormality	3 (2.0)	0
Infection	2 (1.4)	6 (3.9)
Rhinitis	2 (1.4)	4 (2.6)
Dry Mouth	2 (1.4)	1 (0.7)
Vomit	2 (1.4)	1 (0.7)
Anxiety	2 (1.4)	0
Gastritis	2 (1.4)	0
Gastroenteritis	2 (1.4)	0
Pain, Chest	2 (1.4)	0
Palpitation	2 (1.4)	0
Rash Mac Pap	2 (1.4)	0
SGOT Increase	2 (1.4)	0
Flatulence	1 (0.7)	6 (3.9)
Cough Inc	1 (0.7)	3 (2.0)
Rash	1 (0.7)	3 (2.0)
Sinusitis	1 (0.7)	2 (1.3)
Pruritis	0	4 (2.6)
Glossitis	0	2 (1.3)

International Trial

In the international trial, adverse events (AEs) and treatment emergent adverse events (TEAEs) are defined the same as in the North American trial (see above).

One hundred and twenty-nine patients (72.9%) experienced a total of 454 non-serious TEAEs during the study. Most are classified as mild to moderate intensity. All TEAEs are shown in Table 24 in Appendix 4.

There are 12 patients (6.8%) who experienced non-serious TEAEs of severe intensity: three patients with diarrhea (certain (2) and probably/likely), two patients with vomiting (certain and probably/likely), two patients with pain abdominal (both possible), furunculosis (unlikely/unrelated), pyrosis (unlikely/unrelated), hypertonia (unlikely/unrelated), rash (certain), and headache (possible).

There is one patient with four serious TEAEs. Six patients discontinued due to TEAEs.

The incidence of non-serious TEAEs occurring in $\geq 1\%$ of patients in the Safety population is presented in decreasing order of frequency in Table 25 below. Patients are counted only once per preferred term, intensity or relationship category.

Clinical Reviewer's Comment: Possible signs and symptoms of bismuth encephalopathy (e.g., myoclonic jerks, trembling, memory disturbances, confusion and problems of physical coordination) reported for OBMT are: asthenia in 12 patients (6.8%), amnesia in 2 patients (1.1%), spasm general in one patient, and thinking abnormality in one patient. Asthenia was also reported for OAC therapy in the North American study. Based on these events, it is unlikely that 10-days of treatment with Helicide causes bismuth-associated encephalopathy.

**Appears This Way
On Original**

TABLE 25
Most Common ($\geq 1\%$ of Patients) Treatment-Emergent Adverse Events in the Safety Population (N=177), Study HPST99-INT01

Preferred term*	Statistic	TEAEs	Related** TEAEs	Severe TEAEs
Total Number of Patients	n (%)	129 (72.9)	118 (66.7%)	12 (6.8)
STOOL ABNORMALITY	n (%)	63 (35.6%)	63 (35.6%)	0
TASTE PERVERSION	n (%)	39 (22.0%)	39 (22.0%)	0
DIARRHEA	n (%)	38 (21.5%)	35 (19.8%)	3 (1.7%)
NAUSEA	n (%)	34 (19.2%)	33 (18.6%)	0
HEADACHE	n (%)	29 (16.4%)	29 (16.4%)	1 (0.6%)
PAIN ABDOMINAL	n (%)	26 (14.7%)	23 (13.0%)	2 (1.1%)
DYSPEPSIA	n (%)	18 (10.2%)	4 (2.3%)	0
DIZZINESS	n (%)	13 (7.3%)	12 (6.8%)	0
SOMNOLENCE	n (%)	13 (7.3%)	13 (7.3%)	1 (0.6%)
ASTHENIA	n (%)	12 (6.8%)	12 (6.8%)	0
VOMITING	n (%)	11 (6.2%)	10 (5.6%)	2 (1.1%)
FLATULENCE	n (%)	9 (5.1%)	8 (4.5%)	0
URINE ABNORMALITY	n (%)	9 (5.1%)	9 (5.1%)	0
RASH	n (%)	8 (4.5%)	7 (4.0%)	1 (0.6%)
DRY MOUTH	n (%)	7 (4.0%)	7 (4.0%)	0
PAIN	n (%)	7 (4.0%)	5 (2.8%)	0
PHARYNGITIS	n (%)	7 (4.0%)	4 (2.3%)	0
SPEECH DISORDER	n (%)	7 (4.0%)	7 (4.0%)	0
ANOREXIA	n (%)	6 (3.4%)	5 (2.8%)	0
SGPT INCREASE	n (%)	5 (2.8%)	4 (2.3%)	1 (0.6%)
CONSTIPATION	n (%)	4 (2.3%)	4 (2.3%)	0
FLU SYNDROME	n (%)	4 (2.3%)	1 (0.6%)	0
INSOMNIA	n (%)	4 (2.3%)	4 (2.3%)	0
ULCER MOUTH	n (%)	4 (2.3%)	4 (2.3%)	0
DEPRESSION	n (%)	3 (1.7%)	2 (1.1%)	0
ERUCTATION	n (%)	3 (1.7%)	3 (1.7%)	1 (0.6%)
PARESTHESIA	n (%)	3 (1.7%)	2 (1.1%)	0
VAGINITIS	n (%)	3 (1.7%)	3 (1.7%)	0
VASODILATATION	n (%)	3 (1.7%)	3 (1.7%)	0
AMNESIA	n (%)	2 (1.1%)	2 (1.1%)	0
ANXIETY	n (%)	2 (1.1%)	2 (1.1%)	0
BRONCHITIS	n (%)	2 (1.1%)	0	0
DISCOLOR TONGUE	n (%)	2 (1.1%)	2 (1.1%)	0
GI DISORDER	n (%)	2 (1.1%)	2 (1.1%)	0
HEMORRHAGE GI	n (%)	2 (1.1%)	2 (1.1%)	0
HYPESTHESIA	n (%)	2 (1.1%)	2 (1.1%)	0
PALPITATION	n (%)	2 (1.1%)	1 (0.6%)	1 (0.6%)
PYROSIS	n (%)	2 (1.1%)	1 (0.6%)	1 (0.6%)
SALIVA INCREASED	n (%)	2 (1.1%)	2 (1.1%)	0

*coded using the COSTART dictionary

**defined as certain, probably/likely, or possible

2. Adverse Events by Relationship to Treatment

North American Trial

Of the 212 TEAEs reported with OBMT, 207 are judged in relation to study drug. In the OAC group, 235/236 are judged in relation to study drug.

Of the 207 events in the OBMT group, 123 are deemed related to study drugs (i.e., certain, probably/likely, or possible) and 84 are deemed unrelated or unassessable. The most frequently (>5%) reported adverse events deemed related are: stool abnormality (15.6%), nausea (8.2%), diarrhea (6.8%), and headache (5.4%).

Of the 235 events in the OAC group, 139 were deemed related to study drugs with OAC and 96 are deemed unrelated or unassessable. The most frequently (> 5%) reported adverse events are diarrhea (13.2%), taste perversion (11.8%), nausea (9.2%), dyspepsia (5.95), and headache (5.3%).

TEAEs by relationship to study therapy are shown in Table 26 in Appendix 3.

International Trial

One hundred and eighteen (118) patients out of 177 (66.7%) in the safety population reported at least one event that is judged to be related to study medication (i.e., certainly, probably/likely, or possibly). There is one event (flu syndrome) in which the relationship to study medication could not be assessed. The most common ($\geq 5\%$) non-serious TEAEs related to study medication are stool abnormality, taste perversion, diarrhea, nausea, headache, pain abdominal, dizziness, somnolence, asthenia, vomiting, flatulence, and urine abnormality.

TEAEs related to study therapy are shown in Table 25 above.

3. Adverse Events by Subgroup (Age, Gender and Ethnicity)

A summary of demographic characteristics for patients in the safety population for the North American (HPST-CUS01) and International (HPST99-INT01) trials is shown in Table 27 below. The treatment groups in the North American trial were generally well balanced with respect to demographic characteristics.

Clinical Reviewer's Comment: Table 27 was created by the reviewer.

TABLE 27
Demographic Characteristics
Studies HPST99-CUS01 and HPST99-INT01

Characteristic		North American Trial [N=299] (HPST99-CUS01)		International Trial [N=177] (HPST99-INT01)
		OBMT [N=147]	OAC [N=152]	OBMT
Age	< 65 years	131	130	153
	≥ 65 years	16	22	24
Gender	Male	90	87	105
	Female	57	65	72
Race*	Caucasian	84	92	158
	Black	21	12	6
	Asian	11	4	10
	Other	31	44	3

* race classification code was not recorded for one patient in the North American trial

North American Trial

The most frequently reported adverse events (> 6% incidence overall in either treatment group) by age (< 65 and ≥ 65), gender, and race (Caucasian, Black, Asian, Other) are shown below in Table 28A and 28B.

As seen in Table 28A, females have a higher incidence of diarrhea and headache compared to males. This greater frequency was observed in both the OBMT and OAC treatment groups. There is a slight shift in the incidence per treatment for dyspepsia between males and females. Males have a lower incidence of dyspepsia in the OBMT group (6.7%) compared to the OAC group (11.5%). Females have a higher incidence in the OBMT group (12.3%) compared to the OAC group (10.8%). Also while males and females in the OBMT group have a similar incidence of taste perversion, a higher percentage of females in the OAC group (16.9%) compared to the OBMT group (1.8%) experienced this event. However, these differences are slight and unlikely to result in clinically meaningful differences.

As seen in Table 28B, for the gender and race analyses, the numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn.

TABLE 28A
Number (%) of Patients with Frequently Reported Adverse Events by Gender
Safety Population (N=299)
HPST99-CUS01

Reported Adverse Event	Males		Females	
	OBMT (N=90)	OAC (N=87)	OBMT (N=57)	OAC (N=65)
	Stool Abnormality	14 (15.6%)	3 (3.4%)	9 (15.8%)
Diarrhea	6 (6.7%)	11 (12.6%)	7 (12.3%)	12 (18.5%)
Dyspepsia	6 (6.7%)	10 (11.5%)	7 (12.3%)	7 (10.8%)
Abdominal Pain	8 (8.9%)	9 (10.3%)	5 (8.8%)	6 (9.2%)
Nausea	6 (6.7%)	7 (8.0%)	6 (10.5%)	9 (13.8%)
Headache	6 (6.7%)	5 (5.7%)	6 (10.5%)	6 (9.2%)
Taste Perversion	6 (6.7%)	7 (8.0%)	1 (1.8%)	11 (16.9%)

blank page

TABLE 28B
Number (%) of Patients with Frequently Reported Adverse Events by Age and Race Subgroups
Safety Population (N=299)
HPST99-CUS01

Reported Adverse Event	Age < 65		Age ≥ 65		Caucasian		Black		Asian		Other races	
	OBMT (N=131)	OAC (N=130)	OBMT (N=16)	OAC (N=22)	OBMT (N=84)	OAC (N=92)	OBMT (N=21)	OAC (N=12)	OBMT (N=11)	OAC (N=4)	OBMT (N=31)	OAC (N=44)
Stool Abnormality	22 (16.8%)	3 (2.3%)	1 (6.3%)	4 (18.2%)	18 (21.4%)	6 (6.5%)	3 (14.3%)	1 (8.3%)	1 (9.1%)	--	1 (3.2%)	--
Diarrhea	11 (8.4%)	20 (15.4%)	2 (12.5%)	3 (13.6%)	8 (9.5%)	19 (20.7%)	4 (19%)	19 (20.7%)	--	--	1 (3.2%)	2 (4.5%)
Dyspepsia	13 (9.9%)	16 (12.3%)	0	1 (4.5%)	10 (11.9%)	9 (9.8%)	2 (9.5%)	9 (9.8%)	1 (9.1%)	1 (25%)	--	5 (11.4%)
Abdominal Pain	13 (9.9%)	14 (10.8%)	1 (6.3%)	--	9 (10.7%)	8 (8.7%)	1 (4.8%)	1 (4.8%)	--	1 (25%)	3 (9.7%)	5 (11.4%)
Nausea	11 (8.4%)	14 (10.8%)	1 (6.3%)	2 (9.1%)	7 (8.3%)	8 (8.7%)	3 (14.3%)	3 (14.3%)	--	--	2 (6.5%)	7 (15.9%)
Headache	10 (7.6%)	11 (8.5%)	2 (12.5%)	--	6 (7.1%)	5 (5.4%)	2 (9.5%)	2 (9.5%)	3 (27.3%)	1 (25%)	1 (3.2%)	5 (11.4%)
Taste Perversion	5 (3.8%)	17 (13.1%)	2 (12.5%)	1 (4.5%)	4 (4.8%)	16 (17.4%)	2 (9.5%)	--	1 (9.1%)	1 (25%)	--	1 (2.3%)

International Trial

The most frequently reported adverse events (>10% incidence overall) by age (< 65 and ≥ 65), gender, and race (Caucasian, Black, Asian, Other) are shown below in Table 29.

As seen in Table 29, females have a higher incidence of diarrhea, nausea, headache, and taste perversion compared to males. Males have a higher incidence of dyspepsia compared to females. Although the lack of a control group makes interpretation of these events difficult, the differences are slight and unlikely to result in clinically meaningful differences.

For the gender and race analyses, also seen in Table 29, the numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn.

**Appears This Way
On Original**

TABLE 29
Number (%) of Patients with Frequently Reported Adverse Events by Gender, Age and Race Subgroups
OBMT Safety Population (N=177)
HPST99-INT01

Reported Adverse Event	Males		Females		Age < 65		Age ≥ 65		Caucasian		Black		Asian		Other races	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Stool Abnormality	37	(35.2%)	26	(36.1%)	54	(35.5%)	9	(37.5%)	54	(34.2%)	2	(33.3%)	4	(40.0%)	3	(100%)
Diarrhea	16	(15.2%)	22	(30.6%)	30	(19.6%)	8	(33.3%)	36	(22.8%)	1	(16.7%)	--	--	1	(33.3%)
Dyspepsia	13	(12.4%)	5	(6.9%)	16	(10.5%)	2	(8.3%)	18	(11.4%)	--	--	--	--	--	--
Abdominal Pain	15	(14.3%)	11	(15.3%)	20	(13.1%)	6	(25.0%)	23	(14.6%)	1	(16.7%)	1	(10.0%)	1	(33.3%)
Nausea	17	(16.2%)	17	(23.6%)	26	(17.0%)	8	(33.3%)	32	(20.3%)	1	(16.7%)	1	(10.0%)	--	--
Headache	9	(8.6%)	20	(27.8%)	25	(16.3%)	4	(16.7%)	25	(15.8%)	1	(16.7%)	3	(30.0%)	--	--
Taste Perversion	17	(16.2%)	22	(30.6%)	31	(20.3%)	8	(33.3%)	31	(19.6%)	2	(33.3%)	4	(40.0%)	2	(66.7%)

Summary of Subgroup Analyses

The results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also have a higher incidence of nausea and taste perversion. Overall, these differences are slight and unlikely to result in clinically meaningful differences.

The numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly and between the various racial subgroups.

4. Discontinuations from Study Due to Adverse Events

North American Trial

One patient discontinued from the study due to a TEAE. Patient # 5242 withdrew from study after one day of OAC treatment because of mild nausea and pruritus.

- Patient #5242, a 39-year-old male, started treatment with OAC on January 6, 2000. On the same day he developed mild nausea and pruritus. The investigator suspected hypersensitivity to drugs and stopped the treatment. The events resolved in one day without any intervening therapy.

International Trial

There are six patients who discontinued drug therapy due to adverse events, as seen in Table 30 below. Two of these patients experienced events that are judged as certainly related to study medication. Patient #502 was advised to discontinue study treatment after eight days because of a generalized skin eruption (rash) all over her body and Patient #507 stopped her medication after two days because she experienced vomiting.

Clinical Reviewer's Comment: The table below was adapted by the reviewer from a similar table created by the applicant.

TABLE 30
List of Patients Discontinued from Study Treatment Due to Adverse Events
(HPST99-INT01)

Patient #	Preferred Term*	Duration (Days)	Intensity	Relationship to Study Therapy**	Resolution? (Yes/No)
112	Paresthesia	1	Mild	Possible	Yes
	Vomiting	2	Severe	Probably/Likely	Yes
	Diarrhea	3	Severe	Probably/Likely	Yes
121	Dizziness	3	Moderate	Possible	Yes
126	Dizziness	2	Moderate	Probably/Likely	Yes
	Nausea	2	Moderate	Probably/Likely	Yes
	Headache	2	Moderate	Possible	Yes
325	Vomiting	6	Moderate	Possible	Yes
	Diarrhea	7	Severe	Certain	Yes
	Anorexia	4	Moderate	Possible	Yes
	Headache	2	Moderate	Possible	Yes
502	Headache	11	Moderate	Probably/Likely	Yes
	Insomnia	11	Moderate	Probably/Likely	Yes
	Stomatitis	12	Moderate	Certain	Yes
	Asthenia	17	Moderate	Certain	Yes
	Anorexia	11	Moderate	Possible	Yes
	Nausea	11	Moderate	Certain	Yes
	Stool abnormality	11	Moderate	Certain	Yes
	Urine abnormality	11	Moderate	Certain	Yes
	Amnesia	36	Mild	Probably/Likely	Yes
	Diarrhea	8	Severe	Certain	Yes
	Rash	5	Severe	Certain	Yes
507	Headache	-	Moderate	Probably/Likely	No
	Stool abnormality	2	Mild	Certain	Yes
	Taste perversion	2	Mild	Certain	Yes
	Vomiting	2	Severe	Certain	Yes
	Diarrhea	1	Mild	Certain	Yes
	Asthenia	-	Moderate	Certain	No
	Flatulence	-	Moderate	Certain	No
	Pain abdominal	-	Moderate	Certain	No

*coded using the COSTART dictionary

**defined as certain, probably/likely, possible, or unlikely/unrelated

There are two patients who temporarily interrupted study medication due to non-serious TEAEs. Patient #418 experienced vomiting of moderate intensity on the same day when she experienced the serious AEs (noted below in the section on Non-fatal Serious Adverse Events). The event is judged as possibly related to study medication, which was temporarily interrupted due to the event. Patient #434 experienced nausea, tachycardia, and anxiety of

moderate intensity. The events are probably/likely related to study medication, which was temporarily interrupted due to these events.

5. Deaths

One patient died in the course of the clinical development program 12 days after completing treatment in the North American trial (HPST99-CUS01).

- Patient #807, a 75-year old man with history of lung cancer, was randomized into the trial in December 1999 in New Brunswick, Canada. He was treated with OBMT from December 8 to 17, 1999. On [REDACTED] he came to the emergency room complaining of shortness of breath. He was found to have pneumonia in the left upper and lower lobes of the lung, and atelectasis of the right upper lobe. He was also diagnosed with atrial fibrillation and pulmonary edema. He was intubated and transferred to ICU. The patient remained in the ICU until [REDACTED] and was then transferred to a hospital floor. His condition deteriorated and he was transferred back to the ICU. The patient died on [REDACTED]. The cause of death was listed as respiratory failure secondary to pneumonia and pulmonary fibrosis. The investigator judged the patient's death as unlikely to be related to study medication.

Clinical Reviewer's Comment: Agree with the investigators' assessment. It is unlikely that this patient's death was related to study drug.

6. Non-Fatal Serious Adverse Events

North American Trial

There was one patient in the OBMT group (#4804) that experienced a non-fatal serious AE.

- Patient #4804, a 66-year old man with an active duodenal ulcer, was randomized into the trial in California. He was treated with OBMT from October 14 to 23, 1999. A post-treatment ¹³C-UBT on November 22, 1999 was negative. On [REDACTED] he came to the emergency room and a diagnosis of a GI bleed was made. He was hospitalized and treated with omeprazole and famotidine. He recovered and was discharged from the hospital on [REDACTED]. On [REDACTED] he was re-admitted to the hospital due to a near syncopal episode. He was treated for pneumonia and bronchitis with amoxicillin and discharged on [REDACTED]. A second ¹³C-UBT on January 6, 2000 was also negative. The investigator judged the events as unlikely to be related to study medication.

International Trial

One patient (#418), a 37-year old female experienced a total of four serious adverse events (anxiety, hyperventilation, nausea, and pain abdominal) on the fourth day of the treatment regimen. She was admitted to the hospital complaining of worsening nausea, abdominal pain, dry retching, with associated anxiety and hyperventilation. The patient had a history of depression and anxiety for which she had been prescribed citalopram and oxazepam (prn). She also had a history of abdominal pain, dry retching and nausea since an umbilical surgery 4 months earlier. The patient was kept in the hospital overnight for observation and released the next day. The events resolved after treatment with prochlorperazine and hyoscine. She temporarily interrupted study medication for two days but resumed

medication the day following discharge from the hospital and completed the study. All four events are of moderate intensity, and possibly related to study medication.

Clinical Reviewer's Comment: This patient had a history of anxiety and nausea. Therefore, her symptoms could be construed as a worsening of a pre-existing condition and not new events emerging during therapy.

7. Pregnancy

No patient became pregnant, as evidenced by negative pre- and post-therapy pregnancy tests, while receiving study medication in either the North American or International trials.

8. Clinical Laboratory Evaluations

North American Trial

Laboratory tests for hematology, serum chemistry and urinalysis were performed at baseline and at the end of the study (i.e., between 29 and 35 days after the end of treatment).

Patients in both treatment groups experience increases in ALT and AST levels. When individual patient data are reviewed, however, only three patients are considered to have clinical significant findings by the investigators in the OBMT group while no patient is considered to have a clinically significant finding in the OAC group.

- Patient #201 presented for an end of study visit (four weeks after having taken the last study medication) and reported having had an episode of nausea, vomiting, and dizziness. Laboratory results showed elevated transaminases (ALT 96 U/L, normal range 0-40; AST 68 U/L, normal range 0-38). An immediate repeat of these tests confirmed the elevations (ALT, 160; AST, 85). No intervening therapy was prescribed. Two months later ALT was 72 U/L and AST was 39 U/L. The condition was considered resolved.
- Patient #1112 presented with a mild increase in ALT at the end of study visit (four weeks after having taken the last study medication). ALT was 107 U/L from a baseline of 41 U/L (normal range, 0-40 U/L). With no intervening therapy, the test was repeated in one week and the ALT was 64 U/L. The condition was considered resolved.
- Patient #3409 presented with a mild increase in ALT at the end of study visit (four weeks after having taken the last study medication). The ALT was 86 U/L, up from a baseline of 46 U/L (normal range, 0-40 U/L). With no intervening therapy, the test was repeated in two weeks and the ALT was 62 U/L. The condition was considered resolved.

No other clinically relevant trends in laboratory tests were observed.

Clinical Reviewer's Comment: The reviewer agrees with the applicant's assessments.

International Trial

Laboratory tests for hematology, serum chemistry and urinalysis were performed at baseline and at the end of treatment (within four days following completion of therapy).

There were a relatively high number of normal-to-high shifts observed for AST (18.2%) and ALT (25.3%). There are six patients with ALT values $\geq 3 \times$ ULN. Of these patients, four (#330, 409, 423, and 708) have elevated ALT values at baseline which further increased by the end of the 10-day treatment period. The remaining two patients (#120 and 435) have normal liver function tests at baseline. The elevated ALT at the end of treatment visit is reported as a non-serious AE for one patient (Patient #120; possibly related to study drug; no action taken; resolution unknown).

No clinically relevant trends in laboratory tests were observed.

9. Vital Sign And Physical Findings Related to Safety

North American Trial

Physical examination findings and vital sign measurements were performed pre-study and at the end of treatment visit. There were no clinically relevant changes observed in physical exam findings or vital signs. None of the changes were judged to be related to treatment by the investigator or the applicant.

International Trial

Physical examination findings and vital sign measurements were performed pre-study and at the end of treatment visit. There were no clinically relevant changes observed in physical exam findings or vital signs. None of the changes were judged to be related to treatment by the investigator or the applicant.

Clinical Reviewer's Comment: The reviewer agrees with the applicant's assessments.

10. Clinical Pharmacology Studies

In study HLD-PO-241 (a single dose study) there were 23 healthy male subjects included, five of whom did not complete the study. One subject did not return for the first study day (Day 0), three subjects were withdrawn by the investigator for medical reasons, and one subject withdrew consent for personal reasons. There were no withdrawals related to study medication. The number of subjects reporting at least one adverse event by treatment arm are as follows: one in the Helicide fasting group (one AE), 4 in the group receiving the components of Helicide independently (12 AEs), and 7 in the Helicide fed group (9 AEs). Of the AEs judged to be possibly related to treatment, the following occurred more than once across study arms: headache (4 events), increase in ALT (3 events), and dizziness (2 events).

Of the thirty-six (36) healthy male subjects who were included Study HLD-PO-180 (a multiple dose study), thirty-four (34) completed the study. One subject in the Helicide alone arm withdrew consent from the study for personal reasons. One subject in the Helicide + Omeprazole arm was withdrawn due to an adverse event (nausea and vomiting) thought to be related to study drug. The number of subjects reporting at least one adverse event by treatment arm are as follows: 13 in the Helicide alone arm (49 AEs) and 17 in the Helicide + Omeprazole arm (74 AEs). Of the AEs judged to be possibly related to treatment, the following events occurred > 3 times across study arms: headache (12 events), nausea (12 events), abdominal pain (9 events), increase in ALT (9 events), increase in AST (4 events), dizziness (8 events), flatulence (5 events), dyspepsia (5 events), and loose discolored stools (4 events).

Clinical Reviewer's Comment: For a complete description of the design of these studies, see the Clinical Pharmacology and Biopharmaceutics review.

D. Summary of Safety

- In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any AE. For both treatments gastrointestinal AEs are the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache was frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality is a common side effect and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). The applicant noted that "stool abnormality" may refer to the darkening effect of bismuth on the stool and that it may have also been under-reported, since the patients were told *a priori* about this effect. Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.
- Although the safety data from the International trial are not pooled with the North American trial, the results were supportive of each other for OBMT.
- The AEs reported for OBMT therapy in both the North American and International trials do not suggest that patients experienced bismuth-associated neurotoxicity after exposure 10 days of treatment with Helicide.
- In both the North American and the International trials, the number of patients who discontinued due to and AE or experienced a non-fatal TEAEs are low. There are no clinically meaningful differences between treatment groups in the rate of discontinuations due to AEs or non-fatal serious AEs in the North American trial. Discontinuations due to AEs most frequently involve the gastrointestinal system or were allergic-type reactions.
- Only one death occurred in the clinical program and is deemed unlikely to be related to study drug.
- Results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also had a higher incidence of nausea and taste perversion. Overall, these differences are slight and unlikely to result in clinically meaningful differences.
- The numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly and between the various racial subgroups.

- Pediatric patients, patients with renal or hepatic impairment, and pregnant women were specifically excluded from these trials; therefore, it is not possible to comment on the AE profile in these populations.
- In the North American trial, there are no clinically meaningful changes from pre-study to the end of the study visit within or between treatment groups in any of the laboratory parameters analyzed. Both treatment groups appear to experience increases in ALT and AST levels. When individual patient data are reviewed, however, only three patients were considered to have clinical significant findings by the investigators in the OBMT group while no patient is considered to have a clinically significant finding in the OAC group. The clinical relevance of these changes is not known.
- In the International trial, there are no clinically meaningful changes from pre-study to the end of treatment for any of the laboratory parameters analyzed. There are six patients with ALT values $\geq 3 \times$ ULN. The clinical relevance of these changes is not known.
- In the North American and International trials, there are no clinically meaningful changes in any vital sign parameter analyzed.

VIII. Dosing, Regimen, and Administration Issues

The systemic bioavailability of tetracycline is known to be decreased when administered concomitantly with food, milk or cations (e.g., calcium and bismuth salts). However, when bismuth triple therapy is administered for the purposes of *H. pylori* eradication, no provision is made to separate dosing of these two components from each other or from food. Helicide therapy in the current submission was studied in patients instructed to take the Helicide capsule containing the combination of bismuth subsalicylate, tetracycline and metronidazole after meals and at bedtime. In the package insert for Helidac® therapy it also states that the bismuth subsalicylate tablets, tetracycline capsules, and metronidazole tablets should be taken with meals and at bedtime.

Co-administration of tetracycline with food or milk results in binding of the drug to macromolecules found in these substances and results in decreased absorption. Co-administration of tetracycline and cations, including bismuth salts, results in chelation of the two drugs into large complex macromolecules that also are not readily absorbed.

The effect of chelation on anti-*H. pylori* activity has not been well studied. It may be that an interaction between tetracycline and bismuth is beneficial, rather than deleterious, when these two drugs are used in combination for the indication of *H. pylori* eradication, as it may contribute to high intraluminal concentrations in the stomach rather than in the systemic circulation. In a meta-analysis by Chiba et al. (*Am J Gastroenterol* 1992;87:1716-27) the eradication rate for bismuth triple therapy is reported as 94.1% compared to 55.1% for bismuth/metronidazole therapy. Although the studies included in this analysis contain little information describing how tetracycline was administered in relation to bismuth, it is unlikely that patients would have been successful in attempting to administer medications more than four times per day.

In summary, there are no prospectively designed studies published that compare triple therapy with bismuth, tetracycline and metronidazole to dual therapy with bismuth and metronidazole, nor has there been any study published that compares dosing of triple therapy in the presence or absence of food. However, while concomitant administration of tetracycline and food or bismuth salts, as part of the Helicide regimen, may result in decreased systemic absorption of tetracycline, it does not appear to diminish the antibacterial activity of this combination.

IX. Use in Special Populations

Patients with renal or hepatic impairment, pediatric patients, and pregnant women were excluded from the Helicide development program. Metronidazole is metabolized by the liver to a great extent and should be avoided in patients with hepatic impairment. Tetracycline hydrochloride is labeled as Pregnancy Category D due to retardation of skeletal development and embryotoxicity. Therefore, Helicide will be labeled as contraindicated in pregnant (Pregnancy Category D) or nursing women, pediatric patients (under the age of 12 years), and in patients with renal or hepatic impairment.

A. Efficacy

Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories indicate that none of these covariates have a statistically or clinically significant effect on eradication status.

B. Safety

The results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also have a higher incidence of nausea. Overall, these differences are slight and unlikely to result in clinically meaningful differences.

The numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly and between the various racial subgroups.

X. Conclusions and Recommendations

A. Conclusions

In this submission, the applicant demonstrates the activity of Helicide capsules containing biscaltrate potassium, metronidazole, and tetracycline hydrochloride plus omeprazole (Prilosec) capsules (abbreviated OBMT) in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (active or history). The efficacy of OBMT is compared to a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC regimen is an acceptable comparator since it consistently achieves eradication rates of approximately 70% or greater by Modified Intention-to-Treat (MITT) analysis and 80% or greater by Per Protocol (PP) analysis.

The applicant conducted one pivotal Phase III trial in North America (HPST99-CUS01) to document the efficacy of Helicide therapy plus omeprazole. It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -2.1% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are within the recommended range of $\pm 15\%$ and the *H. pylori* eradication rates for the OBMT treatment satisfies the efficacy criteria recommended in the FDA draft *H. pylori* Eradication Guidance.

Overall eradication rates for OBMT therapy in the non-comparative, supportive Phase III international trial are consistent with, although numerically higher than, the results obtained in the OBMT arm in the North American trial for the MITT (92.9% versus 87.7%) and PP (97.3% versus 92.5%) analyses, respectively. These results are similar to other drug therapy trials in which European rates of *H. pylori* eradication are often higher than those seen in North American trials.

Under Section 505(b)(2) of the FD&C Act, the applicant referenced the FDA's findings of safety and effectiveness from NDA 50-719 (Helidac® therapy containing bismuth subsalicylate, metronidazole, and tetracycline for the eradication of *H. pylori*), and literature articles on the efficacy of the combination of omeprazole, bismuth, metronidazole, and tetracycline (OBMT) therapy.

In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any adverse event (AE). For both treatments gastrointestinal AEs were the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality, presumably due to the darkening effect of bismuth on the stool, is a commonly reported AE and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Although the safety data from the International trial are not pooled with the North American trial, the results are supportive of each other with regard to OBMT. The AEs reported for OBMT therapy in both the North American and International trials do not suggest that patients experience neurotoxicity related to bismuth after exposure to Helicide therapy.

B. Recommendations

Therefore, Helicide capsules (biscaltrate potassium + metronidazole + tetracycline HCl), when used in combination with omeprazole, is safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. The recommendation is for approval of Helicide given as three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

Of Note: The Office of Compliance is recommending non-approval of this product due to a failed Prior Approval Inspection (PAI) for the biscalcitrates component.

Joette M. Meyer, Pharm.D.
Clinical Reviewer, DSPIDP, ODE IV, CDER

Ruthanna Davi, M.S.
Statistical Reviewer, DB III, CDER

Concurrence:

HFD-590/TLMO/RocaR
HFD-590/TLStat/HigginsK
HFD-590/DivDir/AlbrechtR
HFD-590/OfficeDir/GoldbergerM

APPENDIX 1 – LITERATURE TABLE (EFFICACY OF OBMT THERAPY)

blank page

TABLE 20
Efficacy of OBMT Therapy - Summary of the Literature

DISCUSSION TABLE

REFERENCE	FIRST AUTHOR	DURATION (DAYS)	Bi-subcitate (mg)	T (mg)	M (mg)	O (mg)	# patients cured	# patients entered	MITT	M sensitive patients cured	M sensitive patients entered	%	M resistant patients cured	M resistant patients entered	%
1 Am J Gastroenterol 1997 Mar;92(3):438-41	KUNG	7	120 qid	500 qid	400 qid	20 bid	50	50	100.0%						
2 Lancet 1995 Apr 13;345(8953):817-20	DE BOER	7	120 qid	500 qid	500 tid	20 bid	53	54	98.1%						
3 Eur J Gastroenterol Hepatol 1995 Dec;7(12):1189-94	DE BOER	7	120 qid	500 qid	500 tid	20 bid	37	40	92.5%						
4 Aliment Pharmacol Ther 1997 Feb;11(1):107-8	VAUTIER	7	120 qid	500 qid	400 S daily	20 bid	48	52	92.3%	48	52	92.3%	32	39	82.1%
5 Gut 1998 Feb;42(2):166-9	VAN DER HULST	7	120 qid	500 qid	500 tid	20 bid	74	82	90.2%	42	43	97.7%			
6 BMJ 1992 Aug 29;305(6852):502-4	HOSKING	7	120 qid	500 qid	400 qid	not specified	70	78	89.7%						
7 DDW abstracts on CD, New Orleans, 1998	DEBOER	7	108 qid	500 qid	250 qid	20 bid	33	37	89.2%						
8 Helicobacter 1996;1:145-50	DE BOER	7	120 qid	500 qid	500 tid	lanso 30 bid	31	35	88.6%						
9 DDW abstracts on disk, Washington, 1997	BOLIN	7	120 qid	500 qid	400 tid	Lanso 30 daily	114	130	87.7%						
10 DDW abstracts on disk, San Francisco, 1996	BORODY	7	120 S daily	250 S daily	200 S daily	20 bid	140	161	87.0%						
11 Lancet 1994 Feb 26;343(8989):508-10	HOSKING	7	120 qid	500 qid	400 qid	20 daily	66	77	85.7%						
12 DDW abstracts on CD, New Orleans, 1998	LAHAIE	7	120 qid	250 qid	250 qid	20 bid	127	161	78.9%	0	0	0.0%	0	0	0.0%
13 J Fam Pract 1996 Dec;43(6):551-5	GOMOLLON	14	120 qid	500 qid	250 tid	20 daily	25	31	80.6%						
14 DDW abstracts on CD, New Orleans, 1998	CHIBA	7	Subsal 524 bid	500 bid	500 bid	20 bid	21	27	77.8%						
15 Gut 1995 Oct;37(4):477-81	BORODY	12	120 S daily	250 S daily	200 S daily	20 bid	122	165	73.9%						
16 Aliment Pharmacol Ther 1997;11:935-8	GRAHAM	10	Subsal 524 bid	500 bid	500 bid	lanso 15 bid	33	46	71.7%	26	29	89.7%	7	17	41.2%
17 DDW abstracts on CD, New Orleans, 1998	GUTIERREZ	14	120 qid	500 qid	500 tid	20 bid	17	24	70.8%						
18 DDW abstracts on CD, New Orleans, 1998	LAHAIE	7	Subsal 524 bid	500 bid	500 bid	20 bid	12	18	66.7%						
19 DDW abstracts on disk, Washington, 1997	MANITZARIS	10	120 qid	500 qid	500 tid	20 bid	38	58	65.5%						
20 Rev Gastroenterol Mex 1998;53(1):21-7	RODRIGUEZ	14	not specified	not specified	not specified	rantidne	41	59	69.5%						
21 World Congress of Gastroenterology, abstracts on CD, Vienna 1998	GRGOV	14	120 qid	500 qid	50 qid	rantidne 500 bid	19	25	76.0%						
22 Helicobacter 1998;3(2):110-4	GOMOLLON	7	120 qid	500 qid	250 tid	20 bid	93	106	87.7%						
23 Helicobacter 1998;3(3):202-5	KORNMANN	7	120 qid	500 qid	400 tid	lanso 10 days	198	219	90.4%						
24 Fam Pract 1999;16(5):483-8	LAI	7	not specified	not specified	not specified	lanso	48	51	94.1%						
25 Alm Pharmacol Ther 2000;14(1):85-9	DEBOER	7	120 qid	250 qid	250 qid	lanso 30 bid	56	65	86.2%						
26 Aliment Pharmacol Ther 2000;14(6):745-50	GRAHAM	14	Subsal 524 tid	500 qid	500 tid	20 daily	24	26	92.3%						
27 DDW abstracts on CD, Orlando, 1999	DEBOER	7	not specified	not specified	not specified	lanso	54	56	96.4%	47	49	95.9%	7	7	100.0%
28 DDW abstracts on CD, Orlando, 1999	KEARNEY	7	subsal	500 qid	250 qid	H2RA	33	38	86.8%						
29 DDW abstracts on CD, Orlando, 1999	KEARNEY	14	subsal	500 qid	250 qid	lanso 30 bid	79	97	81.4%						
30 Med Clin (Barc) 2001;151(1):1-6	GOMOLLON	7	not specified	not specified	not specified	not specified	35	48	72.9%						
31 N Engl J Med 2001;344(13):967-973	CHAN	7	120 qid	500 qid	400 qid	20 daily	389	400	92.3%						
TOTAL							2160	2516	85.9%	163	173	94.2%	70	89	78.7%

**APPENDIX 2 – ADDITIONAL SAFETY TABLES FOR NORTH AMERICAN TRIAL
(HPST99-CUS01)**

blank page

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01)

Preferred Term	Treatment Group		
	Statistic	OBMT	OAC
Number of Patients in the Safety Population	N	147	152
Number of Treatment Emergent Adverse Events	n	212	236
Number of Patients with a Treatment Emergent Adverse Event	n (%)	86 (58.5%)	90 (59.2%)
DIARRHEA	n (%)	13 (8.8%)	23 (15.1%)
DYSPEPSIA	n (%)	13 (8.8%)	17 (11.2%)
STOOL ABNORM	n (%)	23 (15.6%)	7 (4.6%)
NAUSEA	n (%)	12 (8.2%)	16 (10.5%)
PAIN ABDO	n (%)	13 (8.8%)	15 (9.9%)
TASTE PERVERS	n (%)	7 (4.8%)	18 (11.8%)
HEADACHE	n (%)	12 (8.2%)	11 (7.2%)
FLU SYND	n (%)	8 (5.4%)	5 (3.3%)
ASTHENIA	n (%)	6 (4.1%)	4 (2.6%)
PAIN	n (%)	3 (2.0%)	7 (4.6%)
VAGINITIS	n (%)	6 (4.1%)	4 (2.6%)
DIZZINESS	n (%)	5 (3.4%)	4 (2.6%)
CONSTIP	n (%)	2 (1.4%)	6 (3.9%)
INFECT	n (%)	3 (2.0%)	5 (3.3%)
LAB TEST ABNORM	n (%)	4 (2.7%)	4 (2.6%)
FLATUL	n (%)	1 (0.7%)	6 (3.9%)
PHARYNGITIS	n (%)	3 (2.0%)	4 (2.6%)
RHINITIS	n (%)	2 (1.4%)	4 (2.6%)
PAIN BACK	n (%)	3 (2.0%)	2 (1.3%)
COUGH INC	n (%)	1 (0.7%)	3 (2.0%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
PRURITUS	n (%)	0	4 (2.6%)
RASH	n (%)	1 (0.7%)	3 (2.0%)
DRY MOUTH	n (%)	2 (1.4%)	1 (0.7%)
SGPT INC	n (%)	3 (2.0%)	0
SINUSITIS	n (%)	1 (0.7%)	2 (1.3%)
URIN ABNORM	n (%)	3 (2.0%)	0
VOMIT	n (%)	2 (1.4%)	1 (0.7%)
ANEMIA	n (%)	1 (0.7%)	1 (0.7%)
ANXIETY	n (%)	2 (1.4%)	0
FEVER	n (%)	1 (0.7%)	1 (0.7%)
GASTRITIS	n (%)	2 (1.4%)	0
GASTROENTERITIS	n (%)	2 (1.4%)	0
GLOSSITIS	n (%)	0	2 (1.3%)
INFECT URIN TRACT	n (%)	1 (0.7%)	1 (0.7%)
MYALGIA	n (%)	1 (0.7%)	1 (0.7%)
PAIN CHEST	n (%)	2 (1.4%)	0
PALPITAT	n (%)	2 (1.4%)	0
RASH MAC PAP	n (%)	2 (1.4%)	0
RECTAL DIS	n (%)	1 (0.7%)	1 (0.7%)
SGOT INC	n (%)	2 (1.4%)	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
SGPT INC - SGOT INC	n (%)	2 (1.4%)	0
SYNCOPE	n (%)	1 (0.7%)	1 (0.7%)
ABDOMINAL PAIN	n (%)	1 (0.7%)	0
ALLERG REACT	n (%)	0	1 (0.7%)
AMNESIA	n (%)	1 (0.7%)	0
ANEMIA HYPOCHROM	n (%)	0	1 (0.7%)
APNEA	n (%)	1 (0.7%)	0
APPETITE INC	n (%)	1 (0.7%)	0
ARTERIOSCLEROSIS	n (%)	1 (0.7%)	0
ASTHMA	n (%)	0	1 (0.7%)
BILIRUBINEM	n (%)	0	1 (0.7%)
BODY	n (%)	0	1 (0.7%)
BRONCHITIS	n (%)	1 (0.7%)	0
BUN INC	n (%)	0	1 (0.7%)
CREATINE PK INC	n (%)	1 (0.7%)	0
DEHYDRAT	n (%)	1 (0.7%)	0
DEPRESSION	n (%)	1 (0.7%)	0
DUODENITIS	n (%)	1 (0.7%)	0
ENTERITIS	n (%)	1 (0.7%)	0
ERUCTAT	n (%)	0	1 (0.7%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
ESOPHAGITIS	n (%)	1 (0.7%)	0
HEM	n (%)	1 (0.7%)	0
HEM GI	n (%)	1 (0.7%)	0
HEMATURIA	n (%)	0	1 (0.7%)
HERNIA	n (%)	0	1 (0.7%)
HIGH FREQ. BM	n (%)	0	1 (0.7%)
HYPSTHESIA	n (%)	0	1 (0.7%)
HYPOGLYCEM	n (%)	0	1 (0.7%)
HYPOTENS	n (%)	1 (0.7%)	0
IMPOTENCE	n (%)	0	1 (0.7%)
INSOMNIA	n (%)	0	1 (0.7%)
LACERATION L MID FINGER	n (%)	1 (0.7%)	0
LIVER FUNC ABNORM	n (%)	0	1 (0.7%)
MALaise	n (%)	1 (0.7%)	0
MYASTHENIA	n (%)	0	1 (0.7%)
NECK RIGID	n (%)	0	1 (0.7%)
OTITIS EXT	n (%)	0	1 (0.7%)
PAIN BONE	n (%)	0	1 (0.7%)
PAIN EYE	n (%)	1 (0.7%)	0
PAIN HIP	n (%)	0	1 (0.7%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
PNEUMONIA BRONCHITIS	n (%)	1 (0.7%)	0
SOMNOLENCE	n (%)	1 (0.7%)	0
SPASM GENERAL	n (%)	0	1 (0.7%)
SURGICAL REPAIR L MENISCUS	n (%)	1 (0.7%)	0
TACHYCARDIA	n (%)	1 (0.7%)	0
TENDER L UPPER QUADRANT	n (%)	0	1 (0.7%)
TESTIS DIS	n (%)	1 (0.7%)	0
ULCER DUODEN	n (%)	1 (0.7%)	0
ULCER STOMACH	n (%)	1 (0.7%)	0
URIN FREQUENCY	n (%)	1 (0.7%)	0
VASO DILAT	n (%)	0	1 (0.7%)
VIRAL URI	n (%)	1 (0.7%)	0
VISION ABNORM	n (%)	1 (0.7%)	0
VOMIT, PAIN ABDO, DYSPEPSIA	n (%)	1 (0.7%)	0
WBC ABNORM	n (%)	0	1 (0.7%)
WEIGHT INC	n (%)	0	1 (0.7%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
PNEUMONIA BRONCHITIS	n (%)	1 (0.7%)	0
SOMNOLENCE	n (%)	1 (0.7%)	0
SPASM GENERAL	n (%)	0	1 (0.7%)
SURGICAL REPAIR L MENISCUS	n (%)	1 (0.7%)	0
TACHYCARDIA	n (%)	1 (0.7%)	0
TENDER L UPPER QUADRANT	n (%)	0	1 (0.7%)
TESTIS DIS	n (%)	1 (0.7%)	0
ULCER DUODEN	n (%)	1 (0.7%)	0
ULCER STOMACH	n (%)	1 (0.7%)	0
URIN FREQUENCY	n (%)	1 (0.7%)	0
VASO DILAT	n (%)	0	1 (0.7%)
VIRAL URI	n (%)	1 (0.7%)	0
VISION ABNORM	n (%)	1 (0.7%)	0
VOMIT, PAIN ABDO, DYSPEPSIA	n (%)	0	1 (0.7%)
WBC ABNORM	n (%)	0	1 (0.7%)
WEIGHT INC	n (%)	1 (0.7%)	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT			OAC		
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population	(N=299)						
CONSTIP	n (%)	0	2 (1.4%)	0	1 (0.7%)	5 (3.3%)	0
INFECT	n (%)	2 (1.4%)	1 (0.7%)	0	4 (2.6%)	1 (0.7%)	0
LAB TEST ABNORM	n (%)	1 (0.7%)	3 (2.0%)	0	0	4 (2.6%)	0
FLATUL	n (%)	1 (0.7%)	0	0	2 (1.3%)	4 (2.6%)	0
PHARYNGITIS	n (%)	3 (2.0%)	0	0	4 (2.6%)	0	0
RHINITIS	n (%)	2 (1.4%)	0	0	3 (2.0%)	1 (0.7%)	0
PAIN BACK	n (%)	2 (1.4%)	1 (0.7%)	0	1 (0.7%)	1 (0.7%)	0
COUGH INC	n (%)	1 (0.7%)	0	0	2 (1.3%)	1 (0.7%)	0
PRURITUS	n (%)	0	0	0	0	4 (2.6%)	0
RASH	n (%)	0	1 (0.7%)	0	0	3 (2.0%)	0
DRY MOUTH	n (%)	0	2 (1.4%)	0	0	1 (0.7%)	0
SGPT INC	n (%)	0	2 (1.4%)	0	0	1 (0.7%)	0
SINUSITIS	n (%)	1 (0.7%)	0	0	0	0	0
URIN ABNORM	n (%)	1 (0.7%)	2 (1.4%)	0	2 (1.3%)	0	0
VOMIT	n (%)	1 (0.7%)	1 (0.7%)	0	1 (0.7%)	0	0
ANEMIA	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
ANXIETY	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0
FEVER	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
GASTRITIS	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0
GASTROENTERITIS	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories.
 The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

blank page

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT		OAC			
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population	(N=299)						
GLOSSITIS	n (%)	0	0	0	0	2 (1.3%)	0
INFECT URIN TRACT	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
MYALGIA	n (%)	0	1 (0.7%)	0	1 (0.7%)	0	0
PAIN CHEST	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0
PALPITAT	n (%)	2 (1.4%)	0	0	0	0	0
RASH MAC PAP	n (%)	0	2 (1.4%)	0	0	0	0
RECTAL DIS	n (%)	0	1 (0.7%)	0	0	1 (0.7%)	0
SGOT INC	n (%)	0	2 (1.4%)	0	0	0	0
SGPT INC - SGOT INC	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0
SYNCOPE	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
ABDOMINAL PAIN	n (%)	0	1 (0.7%)	0	0	0	0
ALLERG REACT	n (%)	0	0	0	1 (0.7%)	0	0
ANEMIA HYPOCHROM	n (%)	0	0	0	1 (0.7%)	0	0
APNEA	n (%)	1 (0.7%)	0	0	0	0	0
APPETITE INC	n (%)	0	1 (0.7%)	0	0	0	0
ARTERIOSCLEROSIS	n (%)	1 (0.7%)	0	0	0	0	0
ASTHMA	n (%)	0	0	0	1 (0.7%)	0	0
BILIRUBINEM	n (%)	0	0	0	0	1 (0.7%)	0
BODY	n (%)	0	0	0	0	0	0
BRONCHITIS	n (%)	1 (0.7%)	0	0	0	1 (0.7%)	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories.

The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

blank page

blank page

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT			OAC		
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population	(N=299)						
MALaise	n (%)	0	1 (0.7%)	0	0	0	0
MYASTHENIA	n (%)	0	0	0	1 (0.7%)	0	0
NECK RIGID	n (%)	0	0	0	0	1 (0.7%)	0
OTITIS EXT	n (%)	0	0	0	1 (0.7%)	0	0
PAIN BONE	n (%)	0	0	0	0	1 (0.7%)	0
PAIN EYE	n (%)	1 (0.7%)	0	0	0	0	0
PAIN HIP	n (%)	0	0	0	1 (0.7%)	0	0
PNEUMONIA BRONCHITIS	n (%)	1 (0.7%)	0	0	0	0	0
SOMNOLENCE	n (%)	0	1 (0.7%)	0	0	0	0
SPASM GENERAL	n (%)	0	0	0	1 (0.7%)	0	0
SURGICAL REPAIR L	n (%)	1 (0.7%)	0	0	0	0	0
MENISCUS							
TACHYCARDIA	n (%)	0	1 (0.7%)	0	0	0	0
TENDER L UPPER	n (%)	0	0	0	1 (0.7%)	0	0
QUADRANT							
TESTIS DIS	n (%)	1 (0.7%)	0	0	0	0	0
ULCER DUODEN	n (%)	0	1 (0.7%)	0	0	0	0
ULCER STOMACH	n (%)	1 (0.7%)	0	0	0	0	0
URIN FREQUENCY	n (%)	1 (0.7%)	0	0	0	0	0
VASO DILAT	n (%)	0	0	0	0	0	0
VIRAL URI	n (%)	1 (0.7%)	0	0	0	1 (0.7%)	0
VISION ABNORM	n (%)	0	1 (0.7%)	0	0	0	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin. Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy. Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories. The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'.

Adverse events were coded using the COSTART dictionary.
Percentages are based on the number of patients in the Safety Population in each treatment group.

blank page

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT			OAC		
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population	(N=299)						
VOMIT, PAIN ABDO,	n (%)	0	0	0	0	1 (0.7%)	0
DYSPEPSIA	n (%)	0	0	0	0	1 (0.7%)	0
WBC ABNORM	n (%)	0	0	1 (0.7%)	0	0	0
WEIGHT INC							

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin. Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy. Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories. The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'. Adverse events were coded using the COSTART dictionary. Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 28
Adverse Events by Subgroup (Gender, Age, Ethnicity), Study HPST99-CUS01

blank page

**APPENDIX 3 – ADDITIONAL SAFETY TABLES FOR INTERNATIONAL TRIAL
(HPST99-INT01)**

*blank
page* //

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01)

Preferred Term	Statistic		OBMT
	N	n	
Number of Patients in the Safety Population			177
Number of Treatment Emergent Adverse Events			454
Number of Patients with a Treatment Emergent Adverse Event			129 (72.9%)
STOOL ABNORM	n (%)		63 (35.6%)
TASTE PERVERS	n (%)		39 (22.0%)
DIARRHEA	n (%)		38 (21.5%)
NAUSEA	n (%)		34 (19.2%)
HEADACHE	n (%)		29 (16.4%)
PAIN ABDO	n (%)		26 (14.7%)
DYSPEPSIA	n (%)		18 (10.2%)
DIZZINESS	n (%)		13 (7.3%)
SOMNOLENCE	n (%)		13 (7.3%)
ASTHENIA	n (%)		12 (6.8%)
VOMIT	n (%)		11 (6.2%)
FLATUL	n (%)		9 (5.1%)
URIN ABNORM	n (%)		9 (5.1%)
RASH	n (%)		8 (4.5%)
DRY MOUTH	n (%)		7 (4.0%)
PAIN	n (%)		7 (4.0%)
PHARYNGITIS	n (%)		7 (4.0%)
SPEECH DIS	n (%)		7 (4.0%)
ANOREXIA	n (%)		6 (3.4%)
SGPT INC	n (%)		5 (2.8%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.
 Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population.

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic		OBMT
	N	n (%)	
Number of Patients in the Safety Population	177		
CONSTIP	4	2.3%	
FLU SYND	4	2.3%	
INSOMNIA	4	2.3%	
ULCER MOUTH	4	2.3%	
DEPRESSION	3	1.7%	
ERUCTAT	3	1.7%	
PARESTHESIA	3	1.7%	
VAGINITIS	3	1.7%	
VASODILAT	3	1.7%	
AMNESIA	2	1.1%	
ANXIETY	2	1.1%	
BRONCHITIS	2	1.1%	
DISCOLOR TONGUE	2	1.1%	
GIDIS	2	1.1%	
HEM GI	2	1.1%	
HYPESTHESIA	2	1.1%	
PALPITAT	2	1.1%	
PYROSIS	2	1.1%	
SALIVA INC	2	1.1%	
ANAL DIS	1	0.6%	

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.

Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population.

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic	OBMT
Number of Patients in the Safety Population	N	177
ARTHRALGIA	n (%)	1 (0.6%)
BUN INC	n (%)	1 (0.6%)
CONCUSSION	n (%)	1 (0.6%)
DEHYDRAT	n (%)	1 (0.6%)
DERM FUNG	n (%)	1 (0.6%)
DRY EYE	n (%)	1 (0.6%)
DYSURIA	n (%)	1 (0.6%)
ECCHYMOSIS	n (%)	1 (0.6%)
ECZEMA	n (%)	1 (0.6%)
EDEMA PERIPH	n (%)	1 (0.6%)
EDEMA TONGUE	n (%)	1 (0.6%)
EXCESSIVE SUDATION	n (%)	1 (0.6%)
FOOD CRAVINGS	n (%)	1 (0.6%)
FURUNCULOSIS	n (%)	1 (0.6%)
GLOWING CHEEHS	n (%)	1 (0.6%)
GOUT	n (%)	1 (0.6%)
HYPHER GUM	n (%)	1 (0.6%)
HYPERTONIA	n (%)	1 (0.6%)
ITCHY LEG	n (%)	1 (0.6%)
ITCHY ON FACE	n (%)	1 (0.6%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.

Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population.

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic	OBMT
Number of Patients in the Safety Population	N	177
LEUKORRHEA	n (%)	1 (0.6%)
LIVER FUNC ABNORM	n (%)	1 (0.6%)
PAIN BACK	n (%)	1 (0.6%)
PAIN CHEST SUBSTERN	n (%)	1 (0.6%)
PAIN EYE	n (%)	1 (0.6%)
POST-PRAND. PR FULLNESS	n (%)	1 (0.6%)
PRURITUS	n (%)	1 (0.6%)
PURS AND NEEDLES OVER WHOLE BODY	n (%)	1 (0.6%)
RHINITIS	n (%)	1 (0.6%)
SHOCK	n (%)	1 (0.6%)
SPASM GENERAL	n (%)	1 (0.6%)
STOMATITIS	n (%)	1 (0.6%)
SWEAT	n (%)	1 (0.6%)
TACHYCARDIA	n (%)	1 (0.6%)
THINKING ABNORM	n (%)	1 (0.6%)
THROMBOCYTHEM	n (%)	1 (0.6%)
TONGUE DIS	n (%)	1 (0.6%)
TREMOR	n (%)	1 (0.6%)
ULCER DUODEN	n (%)	1 (0.6%)
URIN FREQUENCY	n (%)	1 (0.6%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.
 Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population.

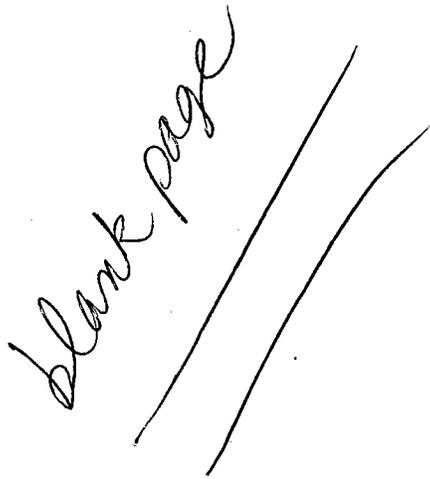
TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic		OBMT
	N	n (%)	
Number of Patients in the Safety Population	177		
VERTIGO		1 (0.6%)	

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.
 Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population.

APPENDIX 4 – INDIVIDUAL REVIEW OF NORTH AMERICAN TRIAL (HPST99-CUS01)

blank page



I. Clinical and Statistical Review of North American Trial (HPST99-CUS01)**Title**

Efficacy and Safety of Quadruple Therapy by Single-Triple Capsules of Biscalcitrates, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *H. pylori*: A Comparison to Omeprazole + Amoxicillin + Clarithromycin (HPST99-CUS01)

Date of Study Initiation: Sept 17, 1999
(First Patient Randomized)

Date of Study Completion: June 22, 2000
(Last Patient Visit)

Date of Report: August 18, 2001

Published Abstracts: Gut 2000;47 Supp1:A100
Gastroenterol 2001;120(3)Supp1:A580

A. Investigators and Study Administrative Structure

There are two principal investigators (PI) for this study: Dr. Loren Laine for the U.S. and Dr. Richard Hunt for Canada. The PIs helped with study design and identification of investigators. Fifty-one (51) sites were recruited and 39 sites randomized at least one patient. Each site had their own investigator and possibly co-investigators. All investigators were certified gastroenterologists.

A single central lab [REDACTED] performed all biochemistry assays for screening procedures and post-treatment safety assessments.

Two pathologists, Dr. Hala El-Zimaity, at Baylor College of Medicine, Houston, for U.S. and Dr. Bich Nguyen at CHUM-Hôpital St-Luc, Montréal for Canada carried all histological confirmations of the presence of *H. pylori* on biopsy slides.

A single microbiologist, Dr. Michael Osato at Baylor College of Medicine, Houston supervised all *H. pylori* cultures and sensitivity assessments.

A single central lab [REDACTED] performed all ¹³C-UBT with a FDA approved test.

The labs [REDACTED], pathologists (Dr. El-Zimaity and Dr. Nguyen), and microbiologist (Dr. Osato) were blinded to treatment received by patients.

B. Study Objectives

The primary objective of this study is to determine the rate of *H. pylori* eradication following therapy with a single capsule (Helicide) containing triple therapy consisting of biscalcitrates, metronidazole, and tetracycline, given with omeprazole (OBMT) in *H. pylori* positive patients with current or history of duodenal ulcer(s).

The secondary objectives of this trial are:

- To document the effect of resistance of *H. pylori* to metronidazole and clarithromycin on the efficacy of these treatments.
- To compare the Helicide plus omeprazole regimen (OBMT) to the FDA-approved regimen of clarithromycin 500 mg, plus amoxicillin 1 gram, plus omeprazole 20 mg (OAC)
- To assess the safety of these therapeutic regimens with respect to adverse events.
- To document the rate of secondary resistance induced by these treatments.

C. Investigational Plan

This is a 56-day, multi-center, randomized, active-controlled, open-label (investigator blinded), parallel group study.

Clinical Reviewer's Comment: Since it is difficult to blind a treatment containing metronidazole (because of the taste) and bismuth (because of the darkening effect on the feces), the Division agreed with the applicant that a double-blind trial would be difficult to conduct. Although the investigators and patients were aware of the treatments, the personnel at the central laboratories who evaluated the biopsy specimens and UBTs, were blinded to treatment. Therefore, the trial is considered blinded for efficacy but open-label for safety.

H. pylori infected patients with one or more endoscopically confirmed duodenal ulcers or a history of duodenal ulcer disease, who met the inclusion criteria, were randomized to one of the following two treatment regimens for 10 days.

- Three (3) Helicide capsules four times daily, after meals and at bedtime plus one omeprazole 20 mg capsule twice a day after breakfast and supper (OBMT).
- One (1) clarithromycin 500 mg tablet plus two amoxicillin 500 mg capsules + 1 omeprazole 20 mg capsule twice a day before breakfast and supper (OAC).

Helicide plus omeprazole treatment (OBMT) was taken after meals, based on the rationale that a prolonged gastric residence time of the drug increases the duration of contact between *H. pylori* and drugs and that may give better eradication rates.

OAC was taken before morning and evening meals, as used in the trials supporting approval of OAC treatment in the U.S.

Each patient, regardless of treatment regimen, also received 100 tablets of Al(OH)_3 antacid (Amphojel®) as rescue medication. These tablets contained 300 mg of Al(OH)_3 and were taken as 2 tablets as needed, a maximum of 4 times daily.

Patients self-administered the study drugs and were instructed not to take the study medications with milk, other dairy products, or antacids.

The following Warnings were made to all patients regardless of their treatment:

- The antacid rescue medication should be taken at least one hour before or two hours after the study medications, since aluminum-, magnesium- or calcium-containing antacids can bind to tetracyclines and interfere with their absorption.

- There is a risk of a disulfiram-like reaction with the combination of alcohol and metronidazole. Therefore, refrain from consuming alcohol during the 10-day treatment period and for the 48 hours following the last dose.
- Women using oral contraceptives: There is a potential decrease in the efficacy of oral contraceptives when used concomitantly with tetracycline (and potentially with other antibiotics). An additional mean of contraception (e.g. condom) is recommended for the rest of the current cycle.
- Avoid exposure to direct sunlight and/or ultraviolet light during the 10-day treatment period and for the 48 hours following the last dose, due to the fact that photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracycline.
- Cisapride, pimozide, and terfenadine are prohibited during the 10- day treatment and for 48 hours following the last dose, due to a potentially dangerous interaction with clarithromycin.

D. Schedule of Visits

Pre-Study Visit(s) (Days -30 to 0)

Upon confirmation of willingness to participate and signature of an informed consent form, each subject began the screening process. Depending on the site's usual procedures, screening assessments could be performed in different order and in one, two, or three visits.

Ideally, at the first visit, after signature of the informed consent form, the patient underwent a ¹³C-urea breath test (¹³C-UBT). Collection of medical history and demographic data, complete physical examination, routine hematology, clinical chemistry, urinalysis, and pregnancy test, if indicated, were also done. If the result of the ¹³C-UBT was positive, the patient could be rescheduled for another Pre-Study visit. A history of duodenal ulcer(s) must be adequately documented by reports from previous endoscopies/X-rays or the presence of an active duodenal ulcer must be documented from the study endoscopy.

Upon confirmation of presence of *H. pylori* by the ¹³C-UBT (about 24 hours after the test), the investigator performed an endoscopy and took 6 biopsies. One antrum biopsy was used for rapid urease test to provide an immediate result as to the presence of *H. pylori*. Three biopsies, two from antrum and one from corpus, were used for histology and two others, one from antrum and one from corpus, for assessment of resistance of *H. pylori* to metronidazole, clarithromycin, amoxicillin, and tetracycline. If the rapid urease test was positive, the patient was assigned a treatment number, in sequential order for the site, and was allowed to start the treatment. The rapid urease test result had to be later confirmed by histology and/or culture to validate the admissibility of the patient.

If a patient started medication on the basis of a positive rapid urease test and was later found *H. pylori* negative by both histology and culture or by ¹³C-UBT alone, he/she was excluded from the modified intent-to-treat (MITT) and efficacy analyses and was considered for safety analysis only. It was left to the investigator's judgement to continue or to stop the 10-day treatment if it was still on-going.

If needed, for logistic and/or practical reasons, all Pre-Study procedures could be done on the same day. In that case, the results of the ^{13}C -UBT were not available before performing the endoscopy. In order to avoid unnecessary procedures and risks for the patient, the investigator must then perform a serologic test that must be positive for *H. pylori* before undergoing the endoscopy.

Also, if needed for practical reasons (i.e. endoscopy performed at a different site than the follow-up), a third pre-study visit could be done. The pre-study procedures were then as follows: Pre-study Visit part 1: as described above. If the ^{13}C -UBT was positive, the patient was referred for endoscopy. Pre-study Visit part 2: endoscopy with rapid urease test and biopsies were performed at the endoscopic site. If the rapid urease test was positive the patient was sent back to the primary care site. Pre-study Visit part 3: the patient came back to the primary care center for his/her drug supply and to start the study.

Study Day 1 was the day when patient started taking the medication. Unless contraindicated, it was recommended that the patient took his/her first dose in the morning. Study Day 1 should not be more than 7 days apart from confirmation of presence of *H. pylori*.

It was possible to perform the endoscopy first, before the ^{13}C -UBT. There then must be medical justifications, other than *H. pylori* detection, to perform the endoscopy. Ideally, the presence of *H. pylori* in this patient had to be documented before endoscopy by serologic testing.

Following successful pre-study evaluations, patients took the medications for 10 days as instructed. Return visits were scheduled as follows:

End-of-Treatment Visit (Days 11-14)

Within 4 days following completion of therapy (i.e. Study Days 11-14), the physical examination and clinical laboratory (hematology, biochemistry and urinalysis) tests done at pre-study were repeated. A pregnancy test was repeated if it had been done at entry. Adverse events and concomitant medication were recorded. Study medications were retrieved at this visit (except for Amphojel).

End-of-Study Visit (At least Day 38)

Between approximately 29 and 35 days after the end of treatment (i.e. Study Days 39-45), patients returned to the study site for a second ^{13}C -UBT and adverse event assessment. Concomitant medications were also recorded. This visit was scheduled as early as possible but not before 29 days after the end of treatment. Patients who did not complete their 10-day treatment could be scheduled to have a repeat ^{13}C -UBT between approximately 29 and 35 days after the time that they would have completed therapy.

If the result of the ^{13}C -UBT was negative, the patient was scheduled for the Confirmation Visit. If the result was positive, the patient underwent a second endoscopy with 2 biopsies for *H. pylori* culture and susceptibility testing to metronidazole and clarithromycin. This patient did not need to undergo the Confirmation Visit and was treated as deemed appropriate by the investigator, outside the scope of the protocol.

Confirmation Visit (At least Day 56)

Between approximately 56 and 63 days after the end of treatment (i.e. Study Days 66-73), patients returned to the study site for a third ¹³C-UBT and adverse event assessment. Concomitant medications were also recorded. This visit was scheduled as early as possible but not before 56 days after the end of treatment.

E. Inclusion Criteria

- Male or non-pregnant female aged 18 to 75 years inclusively.
- Positive for *H. pylori* by:
 - Both ¹³C-UBT and histology
OR
 - Both ¹³C-UBT and culture.
- Current or history (within 5 years) of duodenal ulcer(s) of at least 3 mm documented by endoscopy or radiology.
- Mental and legal ability to give a written informed consent.

F. Exclusion Criteria

- Previous surgery of the stomach such as partial gastrectomy, gastroplasty, or vagotomy. Patients with simple closure of a perforated ulcer or oversewing of a bleeding ulcer may be included.
- Dysphagia or vomiting as major symptoms.
- Any current or recent (within 1 month) hematemesis, melena, or documented gastrointestinal bleeding or iron-deficiency anemia of clinical significance.
- Pregnancy or lactation, or women of childbearing potential not using reliable contraception (i.e., ovariectomy, hysterectomy, tubal ligation for at least 6 months, oral contraceptive, barrier method).
- Inability to abstain from alcohol intake during treatment period.
- Presence of clinically significant impairment of renal function, hepatic function, or liver disease.
- Presence of a contraindication to the use of metronidazole (e.g. active neurological disorder, history of blood dyscrasia, uncorrected hypothyroidism, uncorrected hypoadrenalism, or alcoholism), tetracycline (known sensitivity to tetracyclines), clarithromycin (known hyper-sensitivity to macrolides, use of cisapride, pimozone or terfenadine), amoxicillin (known sensitivity to penicillins), or omeprazole (known sensitivity to omeprazole).
- Presence of other serious medical condition(s) precluding participation.
- Use of antibiotics in the 30 days before enrollment.
- Regular use (> 3 times per week) of bismuth compounds in the 30 days before enrollment.
- Requirement for anticoagulant therapy (except for acetyl-salicylic acid in daily dose of 325 mg or less).
- Use of any experimental drug within the 30 days prior to enrollment.
- Previous attempt with antibiotic treatment to eradicate *H. pylori*.
- Chronic use of anti-ulcer drugs, including H₂ receptor antagonists, sucralfate and prostaglandins during the 1-week period preceding the ¹³C-UBT at enrollment.
- Chronic use of a proton pump inhibitor in the 15 days preceding ¹³C-UBT at entry.
- Patient known to be positive for HIV, hepatitis, or other diseases transmissible by blood or biopsy samples.

- Presence of Zollinger Ellison Syndrome.
- Chronic use of NSAID, except for acetyl-salicylic acid 325 mg or less daily.

Patients were required to discontinue chronic use of PPIs starting at least 15 days prior to enrolment and continuing until the third ¹³C-UBT, done between approximately 56 and 63 days after the end of treatment, except for the omeprazole administered as the study drug. Patients were required to discontinue chronic use of H₂-receptor antagonists starting at least 7 days prior to enrolment and continuing until the third ¹³C-UBT.

In the event that a patient developed a systemic infection (bronchitis, sinusitis, pneumonia, etc.) requiring systemic antibiotic therapy between Study Days 11 and 73, and received antibiotics known to be effective against *H. pylori* (i.e., metronidazole, tetracycline, amoxicillin, clarithromycin, and azithromycin), he/she was excluded from the study. All other antibiotics were evaluated on a case-by-case basis for their known effectiveness against *H. pylori*.

Throughout the study, all chronic medications for dyspepsia, including H₂-receptor antagonists, either by prescription or over the counter, proton pump inhibitors, homeopathy and medicinal herbals were prohibited. Antacids, except bismuth-based products, could be used, but only sporadically if severe dyspepsia was experienced, and the dose was kept to a minimum (2 tablets as needed, a maximum of 4 times daily).

G. Patient Removal

Patients were able to discontinue their participation in the study at any time. In addition, the investigators and the applicant were permitted to discontinue a patient from the study due to development of an adverse event, a significant protocol violation, or if the patient required an immediate medical or surgical procedure that would compromise the patient's continued participation.

H. Other Study Design Features

The study procedures and evaluations were developed in compliance with the then (1999) current guidelines whenever possible:

- DAIDP. Guidance for Industry - Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products. Indication 25: *H. pylori* (FDA, 1997: draft).

Clinical Reviewer's Comment: The Division also shared with the applicant the draft Guidance for Industry – "Reduction of Gastric or Duodenal Ulcer Recurrence by Eradication of H. pylori", which is not available publicly, but which has been shared with other sponsors developing drugs for H. pylori infection.

- Points to Consider when Reviewing Therapeutic Regimens for Eradication of *H. pylori* in GI disease (Health Canada: draft).
- Guidelines for Clinical Trials in *H. pylori* Infection (European *H. pylori* Study Group).
- Canadian *H. pylori* Consensus Conference, Guidelines for the Management of *H. pylori* Infections (American College of Gastroenterology).

I. Diagnostic Methods

¹³C-UBT

Presence or absence of *H. pylori* was assessed by ¹³C-UBT, analyzed at a central lab

Biopsies of Gastric Mucosa

At screening, 6 separate biopsies were taken: 4 from the antrum (1 from the lesser curvature and 3 from the greater curvature) and 2 from the body of the stomach.

One antrum biopsy was used for on-site rapid urease test. Two antrum and one body biopsies were used for histology. *H. pylori* was presumptively identified by its morphology. The presence of tightly coiled spiral organisms (*Gastrospirillum hominis*) was excluded. Slides were read and reported as:

Grade 0	=	<i>H. pylori</i> non-visible (negative)
Grade 1	=	<15 <i>H. pylori</i> per slide
Grade 2	=	1-5 <i>H. pylori</i> per high power field (hpf)
Grade 3	=	6-20 <i>H. pylori</i> / hpf
Grade 4	=	21-100 <i>H. pylori</i> / hpf
Grade 5	=	>100 <i>H. pylori</i> / hpf

One biopsy from the antrum and one from body were used for metronidazole, clarithromycin, amoxicillin and tetracycline susceptibility. *In vitro* antimicrobial susceptibility tests of *H. pylori* isolates to clarithromycin and metronidazole was determined by the agar dilution method. The NCCLS has defined susceptibility to clarithromycin as shown in the following table.

NCCLS Approved Breakpoints for Clarithromycin (Clinical Isolates)
Approved at Subcommittee Level on January 1999

Antibiotic	MIC Range (µg/mL)
Susceptible	≤ 0.25 µg/mL
Intermediate	0.5 µg/mL
Resistant	≥ 1 µg/mL

A minimum inhibitory concentration (MIC) of ≥ 8 µg/mL for metronidazole was defined as resistant.

Clinical Reviewer's Comment: The NCCLS has not standardized testing or agreed upon breakpoints for metronidazole.

If the patient had a positive ¹³C-UBT at the End-of-Study or at the Confirmation Visit, the patient was to be re-endoscoped and two additional biopsies were taken, one from the antrum and one from the body of the stomach, for susceptibility testing against metronidazole and clarithromycin.

J. Efficacy Assessments

A patient was considered to be infected with *H. pylori* at baseline if the rapid urease test was positive and the results were later confirmed by ¹³C-UBT and either histology or culture.

Clinical Reviewer's Comment: The draft Eradication Guidance for Industry recommends a positive result of at least two diagnostic tests, unless there is a positive culture or ¹³C-UBT alone, for inclusion of a patient in the efficacy analyses. The sponsor has chosen a more conservative definition than recommended.

For the determination of the presence of *H. pylori* in biopsies by histology and culture, both antrum and corpus were tested (two biopsies from the antrum and one from the corpus for histology, one biopsy from the antrum and one from the corpus for culture). In the case of discordant results for histology or culture between the antrum and the corpus biopsies, the presence of *H. pylori* was confirmed if at least one of the biopsies was positive for the organism. Uninterpretable results and insufficient tissue sampling were considered to be negative for *H. pylori*.

The main primary efficacy parameter is the absence (eradication) of *H. pylori* after treatment as assessed by ¹³C-UBT. Eradication was defined, according to guidelines, as two negative ¹³C-UBTs done at least 4 weeks (i.e., 28 days) and 8 weeks (i.e., 56 days) after the end of treatment.

K. Statistical Analyses and Evaluability Criteria

Statistical Analyses

The main data analysis performed by the applicant was a Modified Intention-to-treat (MITT) analysis, as requested in regulatory guidelines, which included only patients who met the inclusion/exclusion criteria. A formal efficacy (Per Protocol) analysis was also done.

Clinical and Statistical Reviewers' Comment: The 1997 Guidance document recommends the MITT analysis be considered primary. However, the reviewers, as recommended by the Division, will also consider the consistency, or lack thereof, between the MITT and PP eradication analyses in this review.

The rate of eradication for each treatment was estimated using standard confidence interval methods.

Subgrouping was performed *a posteriori* by susceptibility or resistance to metronidazole and clarithromycin, and 95% confidence intervals were estimated for each subgroup of *H. pylori* strains. For patients randomized to OBMT, the rate of eradication in patients with metronidazole resistant *H. pylori* was compared to that in patients with metronidazole susceptible *H. pylori* by the use of the likelihood ratio test. A similar analysis was done for resistance to clarithromycin in patients randomized to OAC treatment.

A posteriori subgrouping was done by patients with a history of duodenal ulcer in the preceding 2 years and those with a history greater than 2 years and less than or equal to 5 years. The 95% confidence intervals were estimated for each subgroup.

Secondary resistance was evaluated by using descriptive statistics to summarize the shift in susceptibility of strains after treatment.

At FDA's request, an *a posteriori* analysis was also done comparing, for each treatment, the results in patients who have a $\geq 75\%$ drug compliance with those who have a $< 75\%$ drug compliance.

At Health Canada's request, an *a posteriori* analysis was also done on eradication rate where patients with active ulcer disease were isolated from patients with a history of duodenal ulcer ≤ 2 years.

In order to compare the eradication rates obtained with OBMT with those obtained with OAC, a 95% confidence interval was constructed around the difference of 2 proportions.

Since this trial was multi-center, the rate of eradication was generated for each center and compared descriptively. If needed, a unidimensional test for outliers was conducted.

Evaluability Criteria

Subjects who withdrew subsequent to the pre-study evaluations but before receiving any study medication were not included in the database.

Safety Population

All patients exposed to at least one dose of treatment were included in the safety population. Included in this population were those patients who were randomized to and began treatment, but later were declared *H. pylori* negative based on histology and culture results.

Modified Intent-To-Treat (MITT) Population

Patients were excluded from the MITT population if they:

- Were not found to be *H. pylori* positive at screening by both ^{13}C -UBT and histology **OR** both ^{13}C -UBT and culture
- Did not have an adequately documented history of duodenal ulcer or an active duodenal ulcer
- Had any significant exclusion criteria*

* Patients could have been enrolled in the study before results of all pre-study tests were available. These patients were immediately withdrawn upon receipt of these results, if there was any evidence of major violation (e.g. in age, lab results, etc).

**Appears This Way
On Original**

Per Protocol Population

The per protocol population excluded the following patients:

- Those excluded from the MITT population
- Those without results from two post-treatment tests
- Those with protocol deviations*
- Those who took forbidden medications (H₂-receptor antagonist, proton pump inhibitor, antibiotics, etc.)
- Those with ¹³C-UBTs done outside specified time windows [i.e., testing performed earlier than 28 days (first follow-up UBT) or 56 days (second follow-up UBT) after the end of treatment].

*Patients who took any part of the study medication, but failed to complete the course of treatment or the evaluation procedure was considered a dropout and was excluded from the per protocol population.

Clinical Reviewer's Comments: Dropouts during the treatment period where the reason for dropout is related to study medication or progression of disease should be included as failures.

It is recommended in the draft Eradication Guidance that patients who were non-compliant (defined as those who took < 75% of each medication and/or missed > 20% of consecutive doses of each medication) be excluded from the per-protocol population. At the Division's request, the applicant chose instead to do an a posteriori analysis comparing, for each treatment, the eradication results from patients who had a ≥ 75% drug compliance with those who had < 75% drug compliance.

L. Results

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

1. Investigators

There were 51 investigator sites recruited for this study. Of those, 39 sites randomized at least 1 patient.

The number of patients enrolled per site and who received at least one dose of study medication (i.e., safety population) can be seen in Table 1 below. The mean number of patients enrolled was 8 per site (range 1-38). _____ has the highest enrollment at 12.7% (38/299) of the total population.

TABLE 1
Patient Enrollment by Site and Treatment Group
Safety Population (HPST99-CUS01)

04		1	1	2
31		1	1	2
05		3	2	5
07		1	1	2
08		5	5	10
09		1	1	2
10		4	7	11
11		6	5	11
12		6	9	15
13		5	3	8
34		2	2	4
35		2	2	4
36		--	1	1
37		7	12	19
38		--	1	1
15		2	3	5
29		2	2	4
39		16	9	25
23		1	--	1
43		3	4	7
19		4	4	8
24		1	--	1
25		2	1	3
45		2	2	4
46		2	1	3
47		1	--	1
48		15	23	38
44		11	16	27
49		9	6	15
52		11	15	26
54		4	2	6
55		3	2	5
26		1	1	2
28		3	2	5
27		1	2	3
21		2	--	2
	TOTALS	147	152	299

2. Patient Accountability

The number of patients who are included (considered evaluable) or excluded (considered non-evaluable) for the safety, MITT, and per protocol populations by treatment is shown in Table 2 according to the reasons for non-evaluability.

Clinical Reviewer's Data Validation Methods

Validation of the efficacy data was performed by reviewing the electronic and line listings of raw data for patients considered not evaluable by the applicant for either MITT or PP

populations. Evaluability for both populations was made according to the draft Eradication Guidance.

In addition, 10% of the evaluable population (N=28) was randomly selected (blinded to treatment) and independently reviewed. The reviewer's assessment of evaluability corresponded to the applicant's for all patients in this sample.

TABLE 2
Disposition of Patients (HPST99-CUS01)

	TOTAL	OBMT	OAC
SUBJECTS SCREENED	783		
- Screening Failure	484		
= Received Drugs (Safety population)	299	147	152
- Excluded from MITT analysis	24	9	15
Found Hp negative after receiving drugs		0	7
No duodenal ulcer (active or history)		8	8
Should have not been treated: abnormal lab tests at entry		1	0
= MITT population	275	138	137
- Excluded from per protocol analysis	31	18	13
¹³ C UBTs done outside time windows		6	3
Lost to follow-up / voluntary withdrawal / death		6	4
Took a forbidden drug		6	5
Withdrawal due to adverse event		0	1
= Per protocol population	244	120	124

A listing of the patients excluded from the MITT and /or PP analyses and the reason for exclusion is included below.

Excluded from the MITT analysis

Found to be Hp negative after receiving drugs

Seven (7) patients in the OAC group were excluded from both the MITT and PP analyses because they received study drugs based on ¹³C-UBT and rapid urease test but were later found *H. pylori* negative by histology and/or culture.

Identification Numbers of Patients Excluded

OBMT	OAC
--	1010, 1109, 1308, 3914, 3923, 4403, 5239

No duodenal ulcer (active or history)

Sixteen (16) patients (8 in each group) were excluded from both the MITT and PP analyses because they were randomized despite absence of active duodenal ulcer or history of duodenal ulcer. This error was the result of misunderstanding of the protocol by some investigators.

Identification Numbers of Patients Excluded

OBMT	OAC
210, 501, 4302, 4316, 5405, 5408, 5410, 5504	202, 502, 504, 4304, 4307, 4310, 4315, 5404

Should not have been treated: abnormal lab tests at entry

One patient randomized to OBMT (#1113) was excluded from both the MITT and PP analyses due to a protocol violation (i.e., significant neutropenia at baseline). He was enrolled prior to the availability of laboratory tests and immediately discontinued when the results became known.

Excluded from the PP Analysis¹³C-UBTs done outside time windows

Nine (9) patients (6 in the OBMT and 3 in the OAC group) were excluded from the PP analysis because their ¹³C-UBT for the End-of-Study or Confirmation Visit was performed outside the allowed time windows [i.e., testing performed earlier than 28 days (end of study visit) or 56 days (confirmation visit) after the end of treatment]. For some patients a repeat visit, done within the window, reconfirmed the results obtained at a previous visit made outside the window. If both tests gave negative results, the visit was considered in compliance with guideline requirements.

Identification Numbers of Patients Excluded

OBMT	OAC
505, 3504, 3742, 4301, 4511, 5235	3908, 4502, 4601

Clinical Reviewer's Comment: Most of the above patients were excluded because their end of study visit was < 28 days after the end of treatment (i.e., roughly 7 days early). The draft Eradication Guidance recommends that patients with a negative test result < 28 days after the end of treatment be excluded from the PP analysis. However, all of these patients had a second follow-up UBT performed 4 weeks later at the confirmation visit and all were negative. These patients could have been considered successes in the PP analysis, but there are only a few patients involved and the impact on the efficacy analysis is minimal. Therefore, the applicant's analysis will not be redone.

Lost to follow-up / voluntary withdrawal / death

In this category there were 10 patients (6 in the OBMT and 4 in the OAC group) who were excluded from the PP analysis.

Identification Numbers of Patients Excluded

OBMT	OAC
3102, 4878, 4893, 5209, 3921, 807 (death)	3918, 4810, 3715, 4883

Clinical Reviewer's Comment: OAC patient #4883 was excluded from the PP analysis and is listed in the lost to follow-ups/voluntary withdrawal category. However, this patient experienced adverse events during treatment (i.e., headaches, nausea, dizziness, and epigastric distress) and is also listed as a discontinuation. Since it appears that the true cause of her discontinuation is AEs related to study medication, she should have been included as a failure in the PP analysis. The impact on the efficacy analysis is minimal. Therefore, the applicant's analysis will not be redone.

Took a forbidden drug

Eleven (11) patients (6 in the OBMT and 5 in the OAC groups) were considered failures for the MITT analysis and excluded from the PP analysis because they took forbidden medications during the study. Explanations are given below in Table 3.

Clinical Reviewer's Comment: The applicant's definition of failures in the MITT analysis was more rigorous than suggested by the draft Eradication Guidance. In the Guidance, the definition of failures for the MITT analysis does not mention those patients who took forbidden medications. Of the six OBMT patients listed in Table 3 below, 4/4 with a follow-up UBT at Day 56 were negative and could have been classified as successes for the MITT analysis. Of the five OAC patients, 3/3 with a follow-up UBT at Day 56 were negative and could have been classified as successes for the MITT analysis.

TABLE 3
Patients Who Used Forbidden Medications During the Study (HPST99-CUS01)

PATIENT #	RECEIVED	FOR
OBMT		
2603	Amoxicillin	Influenza
2801	Pantoprazole	Prophylaxis of heartburn ⁽¹⁾
2804	Omeprazole	Prophylaxis of heartburn ⁽¹⁾
3501	Famotidine	Indigestion
4804	Amoxicillin Omeprazole, Famotidine	Bronchitis Duodenal ulcer
5409	Amoxicillin	Bronchitis
OAC		
701	Norfloxacin	Bladder infection
2802	Pantoprazole	Prophylaxis of heartburn ⁽¹⁾
2803	Pantoprazole	Prophylaxis of heartburn ⁽¹⁾
3503	Clarithromycin and Azithromycin	Sinusitis
3767	Famotidine	Indigestion

⁽¹⁾ The applicant noted that the Investigator at this site routinely gave PPIs after *H. pylori* eradication treatment. He did not notice that PPIs were not allowed in the protocol and treated four patients before the violation was discovered during a monitoring visit.

Withdrawal due to adverse event

One patient in the OAC group (#5242) was excluded from the PP analysis due to an adverse event.

Clinical Reviewer's Comments: Patient #5242 was withdrawn from the study medications after one day due to a possible allergic reaction. Since the adverse event was probably due to the study medication, this patient should have remained in the PP analysis as a failure. The applicant's analyses was recalculated to include this patient (see below). His bacterial isolate was susceptible to clarithromycin pre-treatment.

Other Minor Deviations, not resulting in patient withdrawal

As allowed by the protocol, some patients took occasional doses of PPIs or H₂-receptor antagonists in the days preceding screening. Since these drugs are at risk of causing false negative results (resulting in excluding a valid patient) and not false positive results (resulting in inclusion of a non-valid patient) this was considered a minor deviation by the applicant. If the ¹³C-UBT done at screening was positive (confirmed by histology or culture) the patient was included in the trial.

Clinical Reviewer's Comment: The practice of including patients who took occasional doses of acid-suppressing medications in the 2 weeks prior to screening with a positive screening ¹³C-UBT is considered acceptable.

Despite the exclusion criteria about the use of NSAID, some investigators did not considered COX-2 specific inhibitors as NSAIDs. This was found *a posteriori* by the applicant during monitoring visits. Since NSAIDs cause a safety issue and not an efficacy issue, the applicant did not withdraw these patients.

Clinical Reviewer's Comment: The practice of including patients who took concomitant COX-2 specific inhibitors during the study is considered acceptable.

3. Demographic Characteristics

Patient baseline demographics are presented in Table 4 and ulcer disease history is presented in Table 5 below. Percentages are based on the number of patients in the Safety Population for each treatment group.

TABLE 4
Demographic Characteristics
Safety Population (HPST99-CUS01)

Parameter	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients	N	147	152
Age (years)	n	147	152
	Mean	46.52	47.89
	Std	13.60	14.52
	Median	45.5	47.5
	Min., Max.	19.2, 75.6	18.1, 74.1
Sex			
Male	n (%)	90 (61.2%)	87 (57.2%)
Female	n (%)	57 (38.8%)	65 (42.8%)
Weight (kg)	n	147	152
	Mean	76.06	77.41
	Std	14.53	16.26
	Median	75.0	77.3
	Min., Max.	43.0, 115.9	46.0, 128.2
Height (cm)	n	147	151
	Mean	168.01	167.35
	Std	9.72	9.75
	Median	167.6	167.6
	Min., Max.	144.8, 190.5	142.2, 188.0
Race			
Unknown	n (%)	1 (0.7%)	0
Caucasian	n (%)	84 (57.1%)	92 (60.5%)
Black	n (%)	21 (14.3%)	12 (7.9%)
Asian	n (%)	11 (7.5%)	4 (2.6%)
Other	n (%)	30 (20.4%)	44 (28.9%)

According to Table 5 shown below, 176 patients were randomized on the basis of history of duodenal ulcer. As mentioned previously, 16 patients did not have any active ulcer at baseline, leaving 107 patients randomized with active ulcer at baseline.

TABLE 5
Ulcer Disease History
Safety Population (HPST99-CUS01)

Parameter	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
History of Gastric Ulcer			
Yes	n (%)	20 (13.6%)	20 (13.2%)
No	n (%)	126 (85.7%)	131 (86.2%)
Unknown	n (%)	1 (0.7%)	1 (0.7%)
History of Duodenal Ulcer			
Yes	n (%)	92 (62.6%)	84 (55.3%)
No	n (%)	55 (37.4%)	68 (44.7%)
History of Non-Ulcer Dyspepsia			
Yes	n (%)	16 (10.9%)	30 (19.7%)
No	n (%)	130 (88.4%)	122 (80.3%)
Unknown	n (%)	1 (0.7%)	0

4. Compliance Results

Compliance in the safety population is shown below in Table 6. Approximately 90% of patients in both the OBMT and OAC groups were compliance with study medication, defined as $\geq 75\%$ of capsules taken and based on the number of returned capsules.

TABLE 6
Compliance with Study Medications
Safety Population (HPST99-CUS01)

Treatment	Compliance $\geq 75\%$	Compliance $< 75\%$
OBMT	132 / 147 (89.8%)	15 / 147 (10.2%)
OAC	142 / 152 (93.4%)	10 / 152 (6.6%)

5. Eradication

Overall Eradication

Eradication in the MITT and PP analyses by treatment group can be seen in Table 7 below.

Clinical Reviewer's Comment: Table 7 was created by the reviewer and not the applicant.

TABLE 7
***H. pylori* Eradication at the Day 56 Visit**
Per Protocol and Modified Intention-to-Treat Analyses
(HPST99-CUS01)

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]
Per Protocol	111/120 (92.5) [87.8; 97.2]	108/124 (87.1) [81.2; 93.0]	5.4 [-2.1; 13.0]
Intention-to-Treat	121/138 (87.7) [82.2; 93.2]	114/137 (83.2) [77.0; 89.5]	4.5 [-3.9; 12.8]

***H. pylori* Eradication at Day 56 Visit**
Per Protocol and Modified Intention-to-Treat Analyses
(HPST99-CUS01)

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/125 (86.4) [80.4, 92.4]	6.1 [-1.5, 13.7]
Modified Intention-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

Clinical Reviewer's Comment: There are two patients in the OBMT group and one in the OAC group with discrepant results between the first and second UBT (i.e., the first was negative and the second was positive). Both OBMT patients have follow-up endoscopies. One patient (#4859) had a biopsy obtained for culture during the endoscopy, which later grew *H. pylori*. It is not clear from the other patient's data (#2301) whether a biopsy was obtained and the culture was negative or whether no specimen was obtained. The OAC patient (#3764) refused the endoscopy and withdrew consent.

OBMT achieves numerically higher eradication rates than OAC. The lower bound of the 95% confidence interval of the difference in eradication rates (OBMT minus OAC) is -2.1% and -3.9% for the MITT and PP analyses, respectively.

Clinical Reviewer's Comment: The applicant has followed the FDA draft Guidance for Industry – "Reduction of Gastric or Duodenal Ulcer Recurrence by Eradication of *H. pylori*" in determining efficacy of OBMT. According to the document, the following recommendations are made regarding establishment of an efficacy threshold.

Active controlled studies are strongly recommended and should be powered for statistical equivalence or superiority. The investigational regimen will be considered similar to the approved comparator if the lower bound of the 95% two-sided confidence interval for the difference in eradication rates (investigational regimen minus approved active therapy) lies above -15%.

The sponsor should discuss the choice of comparator regimens well in advance of beginning the study since it is recognized that some FDA approved regimens may be less ideal for comparative trials.

Although not specified in the study protocol, the difference in the *H. pylori* eradication rate between the OBMT and the OAC treatment group (i.e., delta) satisfies the efficacy criteria recommended in the FDA draft Guidance. The 95% confidence intervals for the difference eradication rates for both the MITT and PP analyses are within the recommended range of $\pm 15\%$.

Eradication by Demographic Subgroup

The applicant did not subcategorize eradication rates at the Day 56 visit based on age, gender, or race.

Reviewers' Comment: Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories were performed by the reviewers to determine whether any of these covariates have a significant effect on H. pylori eradication rates. The results indicate that none of these covariates had a statistically or clinically significant effect on eradication status, based on the reviewers' assessment.

Eradication by Antimicrobial Susceptibility

MITT Population

In the OBMT group, metronidazole susceptibility was successfully assessed pre-treatment in 125 strains; 51 (40.8%) strains were resistant to metronidazole and 74 (59.2%) were susceptible.

In the OAC group, clarithromycin susceptibility was successfully assessed pre-treatment in 114 strains; 14 (12.2%) strains were resistant to clarithromycin, none were of intermediate sensitivity, and 101 (87.8%) were susceptible.

Eradication rates based on pre-treatment susceptibility to metronidazole and clarithromycin for the MITT population are shown in Table 8 below.

Reviewer's Comment: Table 8 was created by the reviewer and not the applicant.

TABLE 8
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
MITT Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	Susceptible	Resistant	Difference [95% CI]	Susceptible	Resistant	Difference [95% CI]
OBMT	68/74 (91.9)	41/51 (80.4)	-11.5 [-24.1, 1.0]	ND	ND	ND
OAC	ND	ND	ND	93/101 (92.1)	3/14 (21.4)	-70.7 [-92.8, -48.5]

ND = not done

Statistical Reviewer's Comments: The difference in eradication rates in the OBMT group between metronidazole susceptible and resistant isolates was calculated by the reviewer and found to be 11.5%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OBMT treated subjects, the rate of eradication in the resistant group is no more than 24.1% lower than that of the susceptible group.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates was calculated by the reviewer and found to be 70.7%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OAC treated subjects, the rate of eradication in the resistant group is at least 48.5% lower than that of the susceptible group.

Per Protocol Population

In the OBMT group, metronidazole susceptibility was successfully assessed pre-treatment in 108 strains; 44 (40.7%) strains were resistant to metronidazole and 64 (59.3%) were susceptible.

In the OAC group, clarithromycin susceptibility was successfully assessed pre-treatment in 106 strains; 13 (12.2%) strains were resistant to clarithromycin, none were intermediate, and 93 (87.8%) were susceptible.

Eradication rates based on pre-treatment susceptibility to metronidazole and clarithromycin for the MITT population are shown in Table 9 below.

Reviewer's Comment: Table 9 was created by the reviewer and not the applicant.

TABLE 9
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
PP Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	Susceptible	Resistant	Difference [95% CI]	Susceptible	Resistant	Difference [95% CI]
OBMT	61/64 (95.3)	38/44 (86.4)	-8.9 [-20.3, 2.4]	ND	ND	ND
OAC	ND	ND	ND	88/93 (94.6)	3/13 (23.1)	-71.6 [-94.9, -48.2]

ND = not done

Statistical Reviewer's Comment: The difference in eradication rates in the OBMT group between metronidazole susceptible and resistant isolates was calculated by the reviewer and found to be 8.9%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OBMT treated subjects, the rate of eradication in the resistant group is no more than 20.3% lower than that of the susceptible group.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates calculated by the reviewer and was found to be 71.6%. The 95% confidence interval for the difference in eradication rates affords the conclusion that for OAC treated subjects, the rate of eradication in the resistant group is at least 48.2% lower than that of the susceptible group.

Eradication by Duration of DiseaseMITT Population

In the OBMT group, 15 (10.9%) patients have an active duodenal ulcer, 114 (82.6%) patients have a history of duodenal ulcer \leq 2 years ago and 9 patients (6.5%) have a history of duodenal ulcer $>$ 2 years ago.

In the OAC group, 13 (9.5%) patients have an active duodenal ulcer, 116 (84.7%) patients have a history of duodenal ulcer \leq 2 years ago, and 8 (5.6%) patients have a history of duodenal ulcer $>$ 2 years ago.

Eradication rates for patients with active duodenal ulcers compared to those with a history of ulcer disease for the MITT population are shown in Table 10 by treatment group. Given the small number of patients in the groups with an active ulcer and with a history of duodenal ulcer $>$ 2 years ago, statistical comparisons were not attempted by the applicant.

Clinical Reviewer's Comment: Table 10 was modified by the reviewer from the applicant's original table.

TABLE 10
Eradication Rates (n/N) [95% CI] by Disease History
MITT Population (HPST99-CUS01)

Treatment	Active Duodenal Ulcer	History of Duodenal Ulcer	
		\leq 2 years ago	$>$ 2 and \leq 5 years ago
OBMT	100% (15 / 15)	85.1% (97 / 114) [78.5; 91.6]	100% (12 / 12)
OAC	92.3% (12 / 13) [77.8; 106.8]	82.8% (96 / 116) [75.9; 89.6]	75% (6 / 8) [45.0; 105]

Per Protocol Population

In the OBMT group, 14 (11.7%) patients have an active duodenal ulcer, 97 (80.8%) patients have a history of duodenal ulcer \leq 2 years ago and 9 patients (7.5%) have a history of duodenal ulcer $>$ 2 years ago.

In the OAC group, 12 (9.7%) patients have an active duodenal ulcer, 104 (83.9%) patients have a history of duodenal ulcer \leq 2 years ago, and 8 (6.5%) patients have a history of duodenal ulcer $>$ 2 years ago.

Eradication rates for patients with active duodenal ulcers compared to those with a history of ulcer disease for the PP population are shown in Table 11 by treatment group. Given the small number of patients in the groups with an active ulcer and with a history of duodenal ulcer $>$ 2 years ago, statistical comparisons were not attempted by the applicant.

Clinical Reviewer's Comment: Table 11 was modified by the reviewer from the applicant's original table.

TABLE 11

**Eradication Rates (n/N) [95% CI] by Disease History
PP Population (HPST99-CUS01)**

Treatment	Active Duodenal ulcer	History of Duodenal Ulcer	
		≤ 2 years ago	> 2 and ≤ 5 years ago
OBMT	100% (14 / 14)	90.7% (88/97) [84.9; 96.5]	100% (9/9)
OAC	91.7% (11 / 12) [76.0; 107.3]	87.5% (91/104) [81.1; 93.9]	75% (6/8) [45.0; 105]

Eradication by Compliance

MITT Population

Twenty-one (21) patients (14.9%) were compliant with < 75% of study capsules (10.4% patients in the OBMT group and 6.2% patients in the OAC group). Table 12 shows the effect of compliance on eradication rates. For both groups compliance < 75% results in a numerically lower eradication rate. However, *a posteriori* comparisons by Fisher's test for both treatment groups did not show a statistically significant difference in eradication based on compliance with study medications.

**TABLE 12
Eradication Rates by Compliance to Medications
MITT population (HPST99-CUS01)**

Sub-population	OBMT	OAC
Compliance ≥ 75%	113 / 125 (90.4%)	111 / 129 (86.0%)
Compliance < 75%	8 / 13 (61.5%)	3 / 8 (37.5%)

Per Protocol Population

Thirteen (13) patients (5.6%) were compliant with < 75% of study capsules (7.5% patients in the OBMT group and 3.3% patients in the OAC group). Table 13 shows the effect of compliance on eradication rates. For both groups compliance < 75% results in a numerically lower eradication rate. However, *a posteriori* comparisons by Fisher's test for both treatment groups did not show a statistically significant difference in eradication based on compliance with study medications.

**TABLE 13
Eradication Rates by Compliance to Medications
PP population (HPST99-CUS01)**

Sub-population	OBMT	OAC
Compliance ≥ 75%	104 / 111 (93.7%)	106 / 120 (88.3%)
Compliance < 75%	7 / 9 (77.8%)	2 / 4 (50.0%)

6. Evaluability Status

Baseline *H. pylori* infection status based on results of the three pre-treatment endoscopic tests in the safety population is presented in Table 14. The results of the rapid urease test

were using only for screening purposes and was not a confirmatory test. In addition to the endoscopic tests, all patients were positive by ¹³C-UBT.

TABLE 14
Classification of *H. pylori* Infection
Based on Endoscopic Tests for *H. pylori* at Baseline
Safety Population
(HPST99-CUS01)

Pre-therapy (Baseline) Diagnosis				
Culture	Histology	Rapid Urease Test	OBMT (N=147)	OAC (N=152)
Three tests available				
+	+	+	130	117
+	+	-	0	2
+	-	+	0	1
+	-	-	1	0
-	+	+	15	22
-	-	+	0	1
-	+	-	0	1
-	-	-	0	2
Two tests available				
+	+	N/A	0	0
+	-	N/A	0	0
-	+	N/A	0	0
-	-	N/A	0	2*
+	N/A	+	0	0
+	N/A	-	0	0
-	NA	+	0	0
-	NA	-	0	0
N/A	+	+	1	2
N/A	+	-	0	0
N/A	-	+	0	0
N/A	-	-	0	0
Zero or one test available				
+	N/A	N/A	0	0
-	N/A	N/A	0	0
N/A	N/A	+	0	1
N/A	N/A	-	0	0
N/A	+	N/A	0	0
N/A	-	N/A	0	1**
N/A	N/A	N/A	0	0

* rapid urease test was performed, in addition to culture and histology, but the results were inconclusive for both patients

** rapid urease test was performed, in addition to histology (culture not available), but the results were inconclusive

Clinical Reviewer's Comments: Since endoscopy was only performed in a small subset of patients with a positive UBT post-therapy, a similar table was not created for the post-therapy data.

7. Susceptibility

Among assessable *H. pylori* strains, pre-treatment resistance is 40.7% for metronidazole, 11.5% for clarithromycin, 2.8 % for tetracycline, and 0.4% for amoxicillin.

Changes in susceptibility to clarithromycin and metronidazole were assessed post-treatment in patients who failed eradication. Unfortunately, many patients refused to have a second endoscopy after treatment. Available results for metronidazole and clarithromycin are presented for the MITT population in Table 15 below.

Statistical Reviewer's Comment: Table 15 should be interpreted with caution as the small number of patients for which data are available most likely do not represent the entire original MITT population.

Clinical Reviewer's Comment: Table 15 was adapted from two of the applicant's tables by the reviewer.

TABLE 15
Baseline *H. pylori* Susceptibility Results vs. Eradication Status After Treatment
MITT Population (HPST99-CUS01)

Susceptibility to Metronidazole at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy			Susceptibility to Clarithromycin at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy		
		R	S	M			R	S	M
Resistant	10	5		5	Resistant	11	8		3
Susceptible	6	1		5	Susceptible	8	1	1	6
Missing	1			1	Missing	4	1		3
Total	17				Total	23			

R = resistant; I = intermediate; S = susceptible; M = Missing

Metronidazole: R \geq 8 μ g/mL; S \leq 4 μ g/mL

Clarithromycin: R \geq 1 μ g/mL; I = 0.5 μ g/mL; S \leq 0.25 μ g/mL

Clinical Reviewer's Comment: The applicant defines metronidazole resistance as a MIC \geq 8 μ g/mL.

Instead, the same data can be represented using MIC values as shown in Table 16 below, which was created by the FDA reviewing microbiologist

TABLE 16
Metronidazole Susceptibility Test Results and
Clinical/Bacteriological Outcomes^a for HELICIDE Therapy
(Three HELICIDE® capsules four times a day
plus omeprazole 20 mg twice daily for 10 days)

APPENDIX 5 – PROPOSED LABEL

blank page

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joette Meyer

9/27/2006 10:33:02 AM

MEDICAL OFFICER

This version supersedes the previous version of the Clinical/Statistical
Review of NDA 50-786

Eileen Navarro

9/27/2006 04:59:55 PM

MEDICAL OFFICER

Clinical and Statistical Review for New Drug Application # 50-786

Drug: Helizide® (Single Triple Capsule)*
Biscalcitrates potassium + Metronidazole + Tetracycline HCl

**The applicant originally proposed "Helicide" for the product name, but subsequently changed it to Helizide. DMETS did not recommend the use of the proprietary name "Helicide." DDMAC also found the name "Helicide" objectionable from a promotional perspective.*

Applicant's Proposed Indication: Helizide® Capsules (biscalcitrates potassium, metronidazole, and tetracycline hydrochloride), in combination with omeprazole are indicated for the eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease (active or by history). The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.

General Information:

Regulatory Contact: CanReg Inc. (representing Axcan Scandipharm Inc.)
440 North Lakeshore Drive
Mundelen, IL 60060

Applicant: Axcan Scandipharm Inc. (formerly Axcan Pharma Inc.)
597 Laurier Boulevard
Mont-Saint-Hilaire, QC
Canada J3H 6C4
Telephone: (450) 467-5138
Fax: (450) 467-5857

Submission/Review Dates:

Date of Submission: September 28, 2001; December 19, 2001; July 8, 2002; September 26, 2002; March 31, 2003
Date of Receipt: October 2, 2001; July 10, 2002; September 27, 2002
Date Review Begun: May 8, 2002
Date Review Completed: September 11, 2003

TABLE OF CONTENTS

EXECUTIVE SUMMARY	i
I. RECOMMENDATIONS	1
A. <i>Recommendations on Approvability</i>	<i>i</i>
B. <i>Recommendations on Phase IV Studies and Risk Management Steps</i>	<i>ii</i>
II. SUMMARY OF CLINICAL FINDINGS	11
A. <i>Brief Overview of the Clinical Development Program</i>	<i>ii</i>
B. <i>Efficacy</i>	<i>iii</i>
1. North American Trial (Protocol HPST99-CUS01).....	<i>iv</i>
2. Comparison With Other FDA-approved Regimens.....	<i>v</i>
C. <i>Safety</i>	<i>vii</i>
1. North American Trial (Protocol HPST99-CUS01).....	<i>vii</i>
D. <i>Dosing</i>	<i>viii</i>
E. <i>Special Populations</i>	<i>viii</i>
1. <i>Efficacy</i>	<i>ix</i>
2. <i>Safety</i>	<i>ix</i>
CLINICAL/STATISTICAL REVIEW	10
I. INTRODUCTION/BACKGROUND	10
A. <i>Overview of Drug, Dosage, and Indications</i>	<i>10</i>
B. <i>Important Milestones in Product Development</i>	<i>10</i>
C. <i>Other Relevant Information</i>	<i>11</i>
II. SUMMARY OF CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEW DISCIPLINES	11
A. <i>Chemistry</i>	<i>11</i>
B. <i>Pharmacology/Toxicology</i>	<i>11</i>
C. <i>Clinical Pharmacology/Biopharmaceutics</i>	<i>12</i>
D. <i>Microbiology</i>	<i>14</i>
III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS	15
A. <i>Pharmacokinetics</i>	<i>15</i>
B. <i>Pharmacodynamics</i>	<i>15</i>
IV. DESCRIPTION OF CLINICAL DATA AND SOURCES	16
A. <i>Overall Data</i>	<i>16</i>
B. <i>Table of Clinical Trials</i>	<i>17</i>
V. CLINICAL REVIEW METHODS	17
A. <i>Structure of the Review</i>	<i>17</i>
B. <i>Overview of Materials Consulted in Review</i>	<i>18</i>
C. <i>Overview of Methods Used to Evaluate Data Quality and Integrity</i>	<i>18</i>
D. <i>Evaluation of Financial Disclosure</i>	<i>18</i>
VI. INTEGRATED SUMMARY OF EFFICACY (ISE).....	19
A. <i>Brief Statement of Efficacy Conclusions</i>	<i>19</i>
B. <i>General Approach to Efficacy Review</i>	<i>19</i>
C. <i>Synopsis of Phase III Efficacy Results</i>	<i>20</i>
1. North American Trial (HPST99-CUS01).....	<i>20</i>
2. International Trial - Protocol HPST99-INT01.....	<i>25</i>
D. <i>Other Supportive Efficacy Data</i>	<i>28</i>
1. Pilot Studies.....	<i>28</i>
2. Investigator Sponsored Trials.....	<i>28</i>
3. Agency's Finding of Safety and Efficacy for Helidac® Therapy.....	<i>29</i>
4. Published Literature Review - Contribution of Each Drug to Efficacy.....	<i>30</i>
5. Literature Review – Efficacy of OBM Therapy.....	<i>32</i>
E. <i>Summary of Efficacy</i>	<i>32</i>
VII. INTEGRATED SUMMARY OF SAFETY (ISS).....	35
A. <i>Brief Statement of Safety Conclusions</i>	<i>35</i>

B.	<i>Description of Drug Exposure</i>	35
C.	<i>Methods and Specific Findings of Safety Review</i>	35
1.	Overview of Adverse Events	36
2.	Adverse Events by Relationship to Treatment.....	41
3.	Adverse Events by Subgroup (Age, Gender and Ethnicity).....	41
4.	Discontinuations from Study Due to Adverse Events	48
5.	Deaths	50
6.	Non-Fatal Serious Adverse Events	50
7.	Pregnancy	51
8.	Clinical Laboratory Evaluations	51
9.	Vital Sign And Physical Findings Related to Safety.....	53
10.	Clinical Pharmacology Studies	54
D.	<i>Summary of Safety</i>	54
VIII.	DOSING, REGIMEN, AND ADMINISTRATION ISSUES	56
IX.	USE IN SPECIAL POPULATIONS	56
A.	<i>Efficacy</i>	57
B.	<i>Safety</i>	57
X.	CONCLUSIONS AND RECOMMENDATIONS	57
A.	<i>Conclusions</i>	57
B.	<i>Recommendations</i>	58
	APPENDIX 1 – Literature Table (Efficacy of obmt therapy)	59
	APPENDIX 2 – Additional Safety Tables for North American Trial (HPST99-CUS01) ...	61
	APPENDIX 3 – Additional Safety Tables for International Trial (HPST99-INT01)	74
	APPENDIX 4 – Individual Review of North American Trial (HPST99-CUS01).....	80
I.	CLINICAL AND STATISTICAL REVIEW OF NORTH AMERICAN TRIAL (HPST99-CUS01)	81
A.	<i>Investigators and Study Administrative Structure</i>	81
B.	<i>Study Objectives</i>	81
C.	<i>Investigational Plan</i>	82
D.	<i>Schedule of Visits</i>	83
E.	<i>Inclusion Criteria</i>	85
F.	<i>Exclusion Criteria</i>	85
G.	<i>Patient Removal</i>	86
H.	<i>Other Study Design Features</i>	86
I.	<i>Diagnostic Methods</i>	87
J.	<i>Efficacy Assessments</i>	88
K.	<i>Statistical Analyses and Evaluability Criteria</i>	88
L.	<i>Results</i>	90
1.	Investigators	90
2.	Patient Accountability	92
3.	Demographic Characteristics	96
4.	Compliance Results	98
5.	Eradication	98
6.	Evaluability Status	104
7.	Susceptibility	106
8.	Safety Analyses.....	107
M.	<i>Clinical and Statistical Reviewers' Conclusions of Study HPST99-CUS01</i>	107
	APPENDIX 5 – Proposed Label (9/5/03)	108

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations on Approvability

In this submission, the applicant demonstrates the safety and efficacy of therapy with Helizide capsules containing bismuth subsalicylate, metronidazole, and tetracycline hydrochloride plus omeprazole (Prilosec®) capsules (abbreviated OBMT) in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (active or history). The efficacy of OBMT is compared to a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC regimen is an acceptable comparator since it consistently achieves eradication rates of approximately 70% or greater by Modified Intent-to-Treat (MITT) analysis and 80% or greater by Per Protocol (PP) analysis.

The applicant conducted one pivotal Phase III trial in North America (HPST99-CUS01) to document the efficacy of Helizide plus omeprazole therapy (OBMT). It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT minus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are above a non-inferiority margin of -15% and provide evidence of the efficacy of Helizide plus omeprazole therapy (OBMT) in the treatment of *H. pylori* infection.

Overall eradication rates for OBMT therapy in the non-comparative, supportive Phase III international trial (HPST99-INT01) are consistent with, although numerically higher than, the results obtained in the OBMT arm in the North American trial for the MITT (92.9% versus 87.7%) and PP (97.3% versus 92.5%) analyses, respectively. These results are similar to other drug therapy trials in which European rates of *H. pylori* eradication are often higher than those seen in North American trials.

The applicant has also referenced under Section 505(b)(2) of the FD&C Act the Agency's finding of the safety and effectiveness of Helidac® therapy (bismuth subsalicylate, metronidazole, and tetracycline) plus an H₂-receptor antagonist. The applicant has included the FDA review of Helidac® therapy and literature articles on the efficacy of OBMT therapy.

In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any adverse event (AE). For both treatments gastrointestinal AEs were the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality, presumably due to the darkening effect of bismuth on the stool, is a commonly reported AE and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Although the safety data from the two Phase III trials are not pooled, the results of the International trial are supportive of the North American trial with regard to OBMT. The AEs

reported for OBMT therapy in both the North American and International trials do not suggest that patients experience neurotoxicity related to bismuth after exposure to Helizide therapy.

Therefore, Helizide capsules (biscalcitrates potassium + metronidazole + tetracycline HCl), when used in combination with omeprazole, are safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. The recommendation from the clinical and statistical reviewers is for approval of Helizide given as three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

The applicant received a "not approvable" letter from ODE IV on August 12, 2002 primarily due to deficiencies found by the Office of Compliance upon inspection of the [REDACTED]. The facility was re-inspected on September 8-11, 2003. As a result of the 2003 inspection, the Office of Compliance is recommending non approval of Helizide due to the continued serious cGMP concerns with Schema [REDACTED] and the biscalcitrates component of the drug product.

B. Recommendations on Phase IV Studies and Risk Management Steps

There are no Phase IV commitments recommended at this time.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Development Program

The worldwide clinical development program for Helizide in combination with omeprazole for the eradication of *H. pylori* includes:

- two Phase I (drug-drug interaction) studies
- two Phase III studies (HPST99-CUS01 and HPST99-INT01)

The number of subjects/patients exposed and the duration of exposure to Helizide during clinical development is shown in Table 1 below:

TABLE 1
Extent of Exposure in Helizide Clinical Trials
Number of Subjects/Patients per Treatment

Trial		Duration of Treatment	Number of Subjects/Patients
Phase I	HLD-PO-241	3 doses	23
	HLD-PO-180	6 days	36
Phase III	HPST99-CUS01	10 days	147
	HPST99-INT01	10 days	177
TOTALS			535

Other supportive clinical data includes:

- Two pilot studies using biscalcitrates, metronidazole, and tetracycline (with or without omeprazole) dispensed as separate formulations in a blister pack.
- Four clinical studies sponsored by independent investigators and conducted using a prototype single triple capsule with a slightly different drug content than Helizide. The capsule was administered with or without a proton pump inhibitor and for a varying duration of therapy. In these studies the applicant's role was limited to supplying study drug to the investigators.
- The Agency's finding of safety and effectiveness for Helidac® therapy (bismuth subsalicylate, metronidazole, and tetracycline). Helidac® therapy was approved by the FDA in 1996 in combination with an H₂-receptor antagonist for the treatment of patients with an active duodenal ulcer associated with *Helicobacter pylori* infection.
- Literature review of the efficacy of OBMT therapy.

Clinical Reviewer's Comment: For combination therapy, the regulations require documentation of the contribution of each component to the overall efficacy of the regimen. Helidac and Helizide both contain bismuth, metronidazole, and tetracycline (BMT). Helidac has previously demonstrated the contribution of each component to the efficacy of the overall regimen. Although, Helizide contains biscalcitrates potassium, an NME and a different bismuth salt from what is found in Helidac, there is no clinical difference between the effect of biscalcitrates and other bismuth salts on H. pylori. Therefore, we can rely upon the Agency's finding of safety and efficacy for Helidac to provide supportive information for Helizide. In addition, the reviewer has included additional literature data as background information to support the rationale for using BMT combination therapy to treat H. pylori and to demonstrate the contribution of each component to the efficacy of the Helizide regimen.

B. Efficacy

The applicant conducted two Phase III trials. One trial was conducted in the US and Canada (Protocol HPST99-CUS01). The other Phase III trial is an international trial conducted in Europe, Australia, Canada and the US (Protocol HPST99-INT01).

In the North American trial, patients were randomized to Helizide plus omeprazole (OBMT) or a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC) and enrolled with a history of or current duodenal ulcer. The International trial differed from the North American trial in that all patients received OBMT. There was no comparator arm in the International trial. Also, the population enrolled in the International trial was symptomatic patients with gastrointestinal complaints (i.e., patients with non-ulcer dyspepsia). It was not necessary for these patients to have a history or current duodenal ulcer. The main efficacy endpoint for both trials is the absence (eradication) of *H. pylori* after treatment. Eradication is defined, according to guidelines, as two negative ¹³C urea breath tests (UBTs) done at least 4 and 8 weeks after the end of treatment.

Due to differences in the patient population enrolled in the two trials and the lack of a comparator arm in the International trial, the North American trial is considered pivotal and the International trial is considered supportive. The efficacy data from the International trial will not be discussed in the Executive Summary, but can be found in the Integrated Summary of Efficacy (ISE).

1. North American Trial (Protocol HPST99-CUS01)

The *H. pylori* eradication rates at 8 weeks post-treatment (i.e., Day 56), are displayed for the applicant's Modified Intent-to-Treat (MITT) and Per Protocol (PP) analyses in Table 2. The reviewers are in agreement with the applicant's results.

Clinical and Statistical Reviewers' Comment: Two patients in the OAC group were excluded from the PP population by the applicant due to adverse events possibly related to study medication. The reviewers have included these two patients in the PP population as failures. The table below has been modified to reflect this change.

TABLE 2
***H. pylori* Eradication at Day 56 Visit**
Per Protocol and Modified Intent-to-Treat Analyses
(HPST99-CUS01)

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference (OBMT – OAC)
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]*
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/126 (85.7) [79.6, 91.8]	6.1 [-0.9, 13.7]
Modified Intent-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

* 95% Confidence Interval for the difference in proportions (OBMT- OAC) is calculated using normal approximation to binomial distribution

The applicant has followed the guidance provided by the Division during the development of Helizide for determining efficacy against *H. pylori*. The following recommendations were made to the applicant regarding establishment of an efficacy threshold.

- Active controlled studies are strongly recommended and should be powered for statistical equivalence or superiority. The investigational regimen will be considered similar to the approved comparator if the lower bound of the 95% two-sided confidence interval for the difference in eradication rates (investigational regimen minus approved active therapy) lies above –15%.
- The sponsor should discuss the choice of comparator regimens well in advance of beginning the study since it is recognized that some FDA approved regimens may be less ideal for comparative trials.

The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Although the delta was not specified in the study protocol, the confidence intervals are above the recommended non-inferiority margin of - 15% and therefore provide evidence of the efficacy of Helizide (OBMT) therapy.

2. Comparison With Other FDA-approved Regimens

Other FDA-approved treatment regimens indicated for *H. pylori* eradication in patients with an active or a history of duodenal ulcer are as follows:

Primary Therapy

- Omeprazole 40 mg QD + Clarithromycin 500 mg TID x 2 weeks. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of Omeprazole 20 mg QD is recommended for ulcer healing and symptom relief.
- Bismuth Subsalicylate 250 mg QID + Metronidazole 250 mg QID + Tetracycline 500 mg QID + an H₂-receptor antagonist (at treatment doses for an active duodenal ulcer) x 4 weeks
- Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 gram BID x 2 weeks
- Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 gram BID x 10 days
- Omeprazole 20 mg BID + Clarithromycin 500 mg TID + Amoxicillin 1 gram BID x 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of Omeprazole 20 mg QD is recommended for ulcer healing and symptom relief.
- Esomeprazole 40 mg QD + Clarithromycin 500 mg BID + Amoxicillin 1 gm BID x 10 days

Alternative Therapy*

- Lansoprazole 30 mg TID + Amoxicillin 1 gram TID x 2 weeks

*For those patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.

As seen in Table 3 below, the Per Protocol eradication rates (92.5%) achieved at 8 weeks post-treatment with Helizide plus omeprazole therapy (OBMT) in this submission appear comparable to those observed with other approved therapies. In addition, the eradication rate achieved with OAC in the North American trial (85.7% by Per-Protocol analysis) is consistent with what has been reported previously.

TABLE 3
FDA-Approved *H. pylori* Treatment Regimens

Therapeutic Components of Approved Treatment Regimens	Dosage	Duration of Therapy	Eradication Rates Reported in Phase III Trials (Per-protocol Analysis#)
Bismuth subsalicylate Metronidazole Tetracycline H ₂ -blocker*	2 chewable tablets (525 mg) QID 250 mg QID 500 mg QID ulcer-treatment doses	14 days 14 days 14 days 28 days	77%, 82%, 71%
Clarithromycin (Biaxin) Omeprazole (Prilosec)	500 mg TID 40 mg QD, then 20 mg QD‡	14 days 14 days 14 days (beginning on Day 15)	64%, 74%
Clarithromycin (Biaxin) Amoxicillin Lansoprazole (Prevacid)	500 mg BID 1 gm BID 30 mg BID	10 days 10 days 10 days	84%
Clarithromycin (Biaxin) Amoxicillin Lansoprazole (Prevacid)	500 mg BID 1 gm BID 30 mg BID	14 days 14 days 14 days	86%, 92%
Amoxicillin† Lansoprazole (Prevacid)	1 gm TID 30 mg TID	14 days 14 days	66%, 77%
Clarithromycin (Biaxin) Amoxicillin Omeprazole (Prilosec)	500 mg BID 1 gm BID 20 mg BID, then 20 mg QD‡	10 days 10 days 10 days 18 days (beginning on Day 11)	78%, 84%, 90%
Clarithromycin (Biaxin) Amoxicillin Esomeprazole (Nexium)	500 mg BID 1 gm BID 40 mg QD	10 days 10 days 10 days	84%, 85%
Clarithromycin (Biaxin) Amoxicillin Rabeprazole (Aciphex)	500 mg BID 1 gm BID 20 mg BID	7 days 7 days 7 days	84% [^]

Evaluable patients were defined as having confirmed active or history of (within 2 years) duodenal ulcer disease and *H. pylori* infection at baseline and for whom results were available for the 4-6 week post-treatment visit

* Not included in Helidac[®] (bismuth subsalicylate, metronidazole, and tetracycline tablets/capsules packaged together)

In patients with a history of duodenal ulcer disease

† For patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected

‡ In patients with an ulcer present at the time of initiation of therapy

[^] evaluable patients were defined as having peptic ulcer disease (confirmed active or history of ulcer within 5 years) or symptomatic non-ulcer disease and *H. pylori* infection at baseline and for whom results were available at the 6 week post-treatment visit

C. Safety

The safety database for this NDA contains data on 383 subjects/patients exposed to Helizide plus omeprazole therapy (OBMT) from two clinical pharmacology studies, one pivotal Phase III trial (North American) and one supportive Phase III trial (International).

Due to differences in the patient population in two Phase III trials and the timing of assessments, the safety results for these two trials will not be pooled. The safety data from the International trial and the two clinical pharmacology studies will not be discussed here, but can be found in the Integrated Summary of Safety (ISS).

1. North American Trial (Protocol HPST99-CUS01)

Two hundred and ninety-nine (299) patients (147 in the OBMT group and 152 in the OAC group) were exposed to at least one dose of the study drugs and constitute the safety population in this study. Of these patients, 86/147 (58.5%) in the OBMT group and 90/152 (59.2%) in the OAC group report treatment emergent adverse events (TEAEs). TEAEs are defined as any event not present prior to exposure to study medication or any event already present that worsens in either intensity or frequency following exposure to study medication. In the OBMT group there are 212 TEAEs reported and 236 TEAEs reported in the OAC group.

Among these TEAEs, most are classified as mild to moderate intensity. Only four events are classified as severe in intensity in each group. Two adverse events are classified as serious, one death and one hospitalization; neither was deemed to be associated with study drug.

In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any TEAE. For both treatments gastrointestinal AEs are the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of metronidazole and/or tetracycline. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality is a common side effect and was more common in the OBMT group than the OAC group (15.6% versus 4.6%). The applicant noted that "stool abnormality" may refer to the darkening effect of bismuth on the stool and that it may have also been under-reported, since the patients were told *a priori* about this effect. Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Possible signs and symptoms of bismuth encephalopathy (e.g., myoclonic jerks, trembling, memory disturbances, confusion and problems of physical coordination) reported in the OBMT group are: asthenia in 6 patients (4.1%) and amnesia in one patient. Asthenia is also reported in the OAC group in 4 patients (2.6%). Based on these events, it is unlikely that 10 days of treatment with Helizide causes bismuth-associated encephalopathy.

Patients in both treatment groups experienced increases in ALT and AST levels. When individual patient data are reviewed, however, only three patients meet the applicant's criteria for clinically significant findings in the OBMT group. No patient is considered to have a clinically significant finding, by the applicant's definition, in the OAC group. These changes, however, are not considered to be clinically meaningful.

There are no clinically relevant changes from pre-study to the end of the study visit within or between treatment groups in any of the other laboratory parameters analyzed or in physical exam findings or vital signs.

D. Dosing

The proposed regimen for Helizide therapy is three Helizide capsules administered four times daily after meals and at bedtime given with omeprazole 20 mg twice daily after breakfast and supper for 10 days. The dose of each component contained in one Helizide capsule and the total daily doses are shown below in Table 4.

TABLE 4
Composition of Helizide Capsule and Total Daily Dose of BMT Therapy

	Dose per capsule	Total Daily Dose (12 capsules/day)
Bismuth subcitrate	140 mg (40 mg as Bi ₂ O ₃ equivalent)	1680 mg (480 mg as Bi ₂ O ₃ equivalent)
Metronidazole	125 mg	1500 mg (1.5 gm)
Tetracycline HCl	125 mg	1500 mg (1.5 gm)

Although the applicant did not conduct dose ranging studies in a systematic manner, efficacy data were obtained from two pilot studies, which helped to refine the dosing and duration of treatment. The results from these studies indicate that 1.0 gram of tetracycline per day is insufficient and 14 days of treatment is better than 7 days. A 10-day treatment regimen is proposed for approval and is the duration of therapy selected for study in the Phase III trials based on the approved duration of therapy for the active control arm (OAC therapy). Published treatment guidelines in the United States also recommend at least 10 days of therapy in order to achieve acceptable eradication rates. The proposed daily dose of metronidazole is higher than the 1.0 gram per day used in the pilot studies. The applicant believes the higher dose is more efficacious in the presence of metronidazole-resistant bacterial isolates and is still within the range of doses used in similar regimens in the literature. The 1.0 gram metronidazole dose is within the range of doses approved by the FDA for other indications and proved to be no cause for a safety concern, based upon the applicant's Phase III safety data.

The applicant originally proposed administering the Helizide treatment regimen on an empty stomach (i.e., before meals) in the Phase III trials, as was done in the two pilot studies. The Division questioned the applicant as to the rationale for dosing on an empty stomach, since medications in the FDA-approved Helidac® regimen (bismuth subsalicylate, metronidazole, and tetracycline) are indicated to be taken with meals. It has also been shown that administration of ranitidine bismuth citrate (Tritec®) with food increases eradication rates compared to administration on an empty stomach (Webb, et al. Am J Gastroenterol 1995;90:1273-7). In response, the applicant modified the dosing of Helizide in the Phase III trials to after meals. The rationale is that a prolonged gastric residence time of the capsule, induced by the fed state, increases the duration of contact between the bacteria and the active drug leading to improved eradication rates.

E. Special Populations

Patients with renal or hepatic impairment, pediatric patients, and pregnant women were excluded from the Helizide development program. Metronidazole is metabolized by the liver to a great extent and should be avoided in patients with hepatic impairment. Tetracycline hydrochloride is labeled as Pregnancy Category D due to retardation of skeletal development and embryotoxicity. Therefore, Helizide will be labeled as contraindicated in pregnant (Pregnancy Category D) or nursing women, pediatric patients (under the age of 12 years), and in patients with renal or hepatic impairment.

1. Efficacy

Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories were performed by the reviewers to determine whether any of these covariates had a significant effect on *H. pylori* eradication rates. The results indicate that none of these covariates have a statistically or clinically significant effect on eradication status, based on the reviewers' assessment.

2. Safety

The results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also have a higher incidence of nausea and taste perversion. Overall, these differences are slight and unlikely to result in clinically meaningful differences.

The numbers of patients in the categories of "age > 65 years" or Black, Asian, and other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events between the young and elderly and between the various racial subgroups.

**Appears This Way
On Original**

The applicant would cite the FDA's finding of safety and effectiveness for Helidac® therapy (NDA 50-719) to support their application under Section 505(b)(2) of the FD&C Act. It was also agreed the applicant would only present one adequate and well-controlled clinical trial in their application.

C. Other Relevant Information

At the current time, Helizide capsules are not registered in any other country. A New Drug Submission for Helizide capsules was sent to the Therapeutic Product Directorate in Canada on September 28, 2001 and was approved in March of 2003.

II. Summary of Clinically Relevant Findings from Other Review Disciplines

A. Chemistry

The application is not approvable from the perspective of the chemistry reviewer based on the results of the cGNP inspection.

The non-approval recommendation is based on the following: There are serious cGMP concerns surrounding this application and _____ the manufacturer of the biscalcitrates drug substance. The Office of Compliance inspected the _____ on May 3-7, 2002 and it was re-inspected on September 8-11, 2003. A Form 483 was issued following both inspections. Some of the deficiencies, or similar items, identified in the September 2003 inspection were also identified during the initial May 2002 inspection. It appears that no corrective action was taken to resolve these deficiencies. Under 21 CFR 314.125(b)(1), the deficiencies must be satisfactorily resolved prior to approval. The Office of Compliance's overall recommendation was "withhold."

Of Note: The applicant received a "not approvable" letter from ODE IV on August 12, 2002 primarily due to deficiencies found by the May 2002 inspection.

See complete review by Gene Holbert, Ph.D., Chemistry Reviewer in HFD-590 (DSPIDP) filed with this NDA (50-786).

B. Pharmacology/Toxicology

The non-clinical pharmacology and toxicology reviewer's recommendation is that the application can be approved.

The following is excerpted from the pharmacology/toxicology review filed with this NDA:

The applicant did not conduct non-clinical studies in support of this NDA submission. Metronidazole and tetracycline are approved drug products. The proposed daily dose levels of 1,500 mg metronidazole and 1,500 mg tetracycline are approved therapeutic doses. The dosing duration of 10 days is within the approved dosing duration for each of these drugs. Therefore, non-clinical studies are not necessary for metronidazole and tetracycline.

Biscalcitrates potassium is similar to colloidal bismuth subcitrate (CBS), also referred to as tripotassium dicitrate bismuthate (Bi_2O_3), which is the active ingredient in De-NolTab, an

approved drug product in Europe. Current accepted therapeutic daily doses of CBS in Europe deliver approximately 480 mg equivalents of Bi_2O_3 daily for up to 8 weeks. The proposed daily biscalcitrates potassium dose level expressed as mg equivalents of Bi_2O_3 is approximately 480 mg (i.e., 40 mg equivalents \times 3 tablets \times 4 daily doses). Any potential human toxicity from biscalcitrates potassium would be from excessive systemic concentrations of bismuth, particularly in the brain and central nervous system. There are, however, no indications of bismuth toxicity resulting from CBS therapy at the proposed dose.

A synopsis of pre-clinical animal toxicology data supplied by the applicant indicates that no adverse effects are observed in rats and dogs at each daily oral dose level of biscalcitrates potassium used in six month toxicity studies. The highest dose levels (converted to mg equivalents of Bi_2O_3) are 30 mg/kg and 18 mg/kg for rats and dogs, respectively. These dose levels corresponded to human equivalent doses (based upon relative body surface area) of 4.8 mg/kg and 10 mg/kg (rat and dog studies, respectively). The approximate mg equivalents of Bi_2O_3 per kg body weight for the human dosing regimen is 7 mg/kg (for a 67 kg subject). Also cited are embryo-fetal development studies in rats and rabbits. No maternal and embryo-fetal effects are reported at any of the dose levels examined with the highest dose level in both rats and rabbits being 30 mg equivalents of Bi_2O_3 per kg body weight.

Biscalcitrates potassium can also be directly compared to bismuth subsalicylate (BSS), which is approved for over the counter use in the US as Pepto-Bismol®. The maximum recommended dose for BSS is approximately 4 grams per day, which corresponds to 2.3 grams of bismuth. This level of bismuth is almost 5-fold greater than the mg equivalents of Bi_2O_3 contained in the proposed daily oral dose of biscalcitrates potassium in the Helizide capsules.

In summary, there are no relevant non-clinical safety issues with the clinical use of Helizide for the eradication of *H. pylori*.

See complete review by Steven Hundley, Ph.D., Pharmacology/Toxicology Reviewer in HFD-590 (DSPIDP) filed with this NDA (50-786).

C. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology and biopharmaceutics reviewer's recommendation is that the application can be approved.

The following is excerpted from the clinical pharmacology and biopharmaceutics review filed with this NDA:

The individual pharmacokinetics of bismuth salts, metronidazole, and tetracycline have all been previously reported in the scientific literature. The applicant was requested by the Division to perform three clinical pharmacology studies with Helizide:

1. a comparison of the bioavailability following a single clinical dose of biscalcitrates potassium, plus metronidazole, plus tetracycline hydrochloride formulated as Helizide capsules versus the three drugs given as separate tablets/capsules
2. a food effect study

3. a drug interaction study to compare the bioavailability of bismuth following multiple dose administration of Helizide capsules administered with and without omeprazole.

A bioavailability study was performed to compare administration of bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride formulated as Helizide capsules compared to administration as separate tablets/capsules containing the individual drug products. The results demonstrate low and variable plasma concentrations of tetracycline and bismuth following administration of Helizide capsules compared to the individual tablets/capsules.

The results of the food effect study demonstrate decreased systemic exposure of bismuth, metronidazole, and tetracycline when administered as Helizide capsules with food as compared to fasting.

Despite lower exposure to one or more of the components of the Helizide capsule when administered in the Helizide dosage form or with food, clinical response (i.e., bacterial eradication) was achieved with the Helizide regimen in the clinical development program. The formulation of Helizide used in the pivotal Phase III trial was the same as used in these studies and patients were instructed to take the medication with food. In the Phase III trial the Helizide treatment regimen demonstrates a high eradication rate and statistical non-inferiority when compared to the active comparator regimen comprised of omeprazole, amoxicillin, and clarithromycin (MITT analysis: 87.7% versus 83.2%; point estimate 4.5%, 95% CI -3.9; 12.8). Therefore, local (topical) exposure, and not systemic exposure, may be important for *H. pylori* eradication.

In contrast, exposure to bismuth is increased when Helizide is administered in combination with omeprazole compared to administration of Helizide alone. Although bismuth peak concentrations (C_{max}) were elevated with the combination, they did not exceed the alarm level for causing neurotoxicity. There is no clinical evidence in the literature to suggest that transient high peak concentrations (i.e., C_{max}) are related to toxicity. Rather, it is only sustained steady state concentrations obtained with chronic dosing that have been associated with neurotoxicity. Steady state concentrations of bismuth are obtained after 4 to 5 weeks of chronic dosing whereas the duration of dosing in this study was only 6 days. The recommended treatment regimen of Helizide and omeprazole is indicated for a total of 10 days. Therefore, it is unlikely that patients receiving treatment will achieve steady state concentrations of bismuth. Finally, the study of Helizide with or without omeprazole was performed under fasting conditions and food decreases systemic absorption of bismuth, as discussed above. In clinical practice, patients will be instructed to take Helizide following meals. There are no data available on steady-state concentrations of bismuth following multiple doses of Helizide and omeprazole when dosed with food. However, the adverse events reported in the clinical trial do not suggest that patients experienced bismuth neurotoxicity during therapy.

In summary, alterations in the bioavailability of bismuth, metronidazole, and/or tetracycline after administration of Helizide capsules with food or omeprazole are of limited clinical significance, as supported by the efficacy and safety data obtained with the regimen in the Phase III clinical trial.

See complete review by Joette Meyer, Pharm.D., Clinical Pharmacology /Biopharmaceutics Reviewer in HFD-590 (DSPIDP) filed with this NDA (50-786).

See complete review by Peter A. Dionne, Microbiologist in HFD-590 (DSPIDP) filed with this NDA (50-786).

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The individual pharmacokinetics of bismuth salts, metronidazole, and tetracycline are all well characterized in the scientific literature and will not be discussed here.

B. Pharmacodynamics

Although the applicant did not conduct formal dose ranging studies, efficacy data were obtained from pilot studies using various doses and duration of treatment with bismaltrate, metronidazole, and tetracycline (BMT) triple therapy alone and in combination with a proton pump inhibitor (PPI).

In the applicant's initial pilot study (HP93-C01), 57 patients received a treatment with bismaltrate 120 mg (equivalent to 40 mg Bi_2O_3) + metronidazole 250 mg + tetracycline 500 mg administered four times daily one hour before meals and at bedtime for 14 days. The Helizide capsules was not used. All three drugs were dispensed as separate formulations, packaged together in a blister pack. A control group of 35 patients received matching placebos. Eradication rates in the BMT arm in patients with or without duodenal ulcer(s) or history of duodenal ulcer were 81.5% in the Modified Intention-to-Treat (MITT) analysis and 89.8% in the Per Protocol (PP) analysis.

In an effort to increase efficacy, a second trial (HP97-C01) was undertaken with the addition of a proton pump inhibitor (omeprazole) to the BMT regimen. For patient convenience, the treatment duration was reduced from 14 days to 7 days and the tetracycline dose was reduced from 500 mg to 250 mg four times daily (i.e., 2 grams to 1 gram total daily dose). The dosing regimen in this study was bismaltrate 120 mg (equivalent to 40 mg Bi_2O_3) + metronidazole 250 mg + tetracycline 250 mg QID one hour before meals and at bedtime given with one omeprazole 20 mg tablet 1 hour before the morning and evening meal. As in the first pilot study, the three drugs were dispensed as separate formulations, packaged together in a blister pack. One hundred and sixty-one (161) patients with or without duodenal ulcer or history of duodenal ulcer were evaluable by MITT analysis and 146 by PP analysis. Eradication rates (95% Confidence Interval) were 80% (73.3%-85.7%) and 84% (78.3%-90.2%) for MITT and PP analysis, respectively.

The applicant concluded from these initial two studies that reducing the study duration from 14 days to 7 days and the daily dose of tetracycline from 2.0 grams to 1.0 gram/day was detrimental despite the addition of a PPI. This led to the final doses used in the Phase III trials and the proposed treatment regimen: bismaltrate (equivalent to Bi_2O_3 120 mg) + metronidazole 375 mg + tetracycline 375 mg four times daily after meals and at bedtime given with omeprazole 20 mg twice daily after breakfast and supper for 10 days. A 10 day

treatment regimen was selected for the Phase III trials since this is the duration of therapy for the FDA-approved active control regimen (OAC) and is in agreement with published recommendations regarding duration of treatment. The tetracycline dosage (1.5 grams/day) is higher than in the 7-day study (1.0 gram/day) since the eradication rate fell when this dose was used as compared to the 2.0 gram/day dose in the initial 14-day study. The tetracycline dose in the proposed regimen is limited at 1.5 grams/day by the size of the tetracycline capsule within the Helizide formulation. For most infections, the usual approved daily dose of tetracycline is 1.0 to 2.0 grams/day divided in two or four equal doses for up to four weeks.

The metronidazole dose is increased to 1.5 grams/day from 1.0 gram/day used in the pilot studies. The applicant believes the higher dose is necessary to maintain efficacy in the presence of bacterial isolates with metronidazole resistance. A 1.5 gram/day dose of metronidazole is still within the range of doses used in similar *H. pylori* treatment regimens reported in the literature. In addition, it is less than the 2.25 gram/day dose of metronidazole approved for intestinal amebiasis (given as 750 mg TID for 5 to 10 days).

The applicant originally proposed administering the Helizide treatment regimen in the Phase III trials on an empty stomach (i.e., before meals) as was done in studies HP93-C01 and HP97-C01. The Division questioned the applicant as to the rationale for dosing on an empty stomach, since medications in the Helidac® regimen are indicated to be taken with meals. In addition, it has been shown that administration of ranitidine bismuth citrate (Tritec®) with food increases eradication rates compared to administration on an empty stomach (Webb, et al. Am J Gastroenterol 1995;90:1273-7). In response, the applicant modified the dosing to after meals based on the rationale that a prolonged gastric residence time of the drug, induced by the fed state, increases the duration of contact between *H. pylori* and the active medication leading to improved eradication rates. (Also, see Section VIII on Dosing, Regimen and Administration Issues).

IV. Description of Clinical Data and Sources

A. Overall Data

The worldwide clinical development program for Helizide in combination with omeprazole for the eradication of *H. pylori* includes:

- two Phase I (drug-drug interaction) studies
- two Phase III studies (HPST99-CUS01 and HPST99-INT01)

Other supportive clinical data includes:

- Two clinical trials using bismuth citrate, metronidazole, and tetracycline (with or without omeprazole) dispensed as separate formulations in a blister pack.
- Four pilot clinical studies conducted using a prototype single triple capsule with a slightly different drug content than Helizide. The capsule was administered with or without a proton pump inhibitor and for a varying duration of therapy. These studies were sponsored by independent investigators and the applicant's role was limited to supplying study drug.
- The Agency's finding of safety and effectiveness for Helidac® therapy (bismuth subsalicylate, metronidazole, and tetracycline). Helidac® therapy was approved by

- the FDA in 1996 in combination with an H₂-receptor antagonist for the treatment of patients with an active duodenal ulcer associated with *Helicobacter pylori* infection.
- Literature review of the efficacy of OBMT therapy.

B. Table of Clinical Trials

The applicant conducted two Phase III trials. One trial was conducted in the US and Canada (Protocol HPST99-CUS01). The other Phase III trial was an international trial conducted in Europe, Australia, Canada and the US (Protocol HPST99-INT01). See Table 5 below for number of patients enrolled in the safety population for each trial.

In the North American trial, patients were randomized to Helizide plus omeprazole (OBMT) or a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC) and enrolled with a history of or current duodenal ulcer. The International trial differed from the North American trial in that all patients received OBMT. There was no comparator arm in the International trial. Also, the population enrolled in the International trial is symptomatic patients with gastrointestinal complaints (i.e., patients with non-ulcer dyspepsia). It was not necessary for these patients to have a history or current duodenal ulcer. The main efficacy endpoint for both trials is the absence (eradication) of *H. pylori* after treatment. Eradication is defined, according to guidelines, as two negative ¹³C urea breath tests (UBTs) done at least 4 and 8 weeks after the end of treatment.

TABLE 5
Helizide Phase III Clinical Trials

Trial	Location	Duration of Treatment	Number of Patients (Safety Population)		Total
			Helizide	Control	
HPST99-CUS01	US and Canada	10 days	147	152	299
HPST99-INT01	Europe, Australia, Canada, and US	10 days	177	--	177
TOTALS			324	152	535

V. Clinical Review Methods

A. Structure of the Review

For the purpose of this application, one North American Phase III trial (HPST99-CUS01) is considered pivotal. The International Phase III trial (HPST99-INT01) is considered supportive. This decision is based on the fact that there are differences in the patient population enrolled in the two trials (ulcer disease versus non-ulcer dyspepsia) and the International trial lacks a comparator arm.

B. Overview of Materials Consulted in Review

Material Submitted: 67 Volumes
Electronic data, including SAS transport files
\\CDSESUB1\N50786\N 000\2001-09-28
\\CDSESUB1\N50786\N 000\2001-12-19

Material Reviewed: Volume 1 and Volumes 31 through 42, 64 and 67
Electronic data, including SAS transport files
\\CDSESUB1\N50786\N 000\2001-09-28
\\CDSESUB1\N50786\N 000\2001-12-19

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested for this trial.

Clinical Reviewer's Comment: A routine DSI audit was not felt to be necessary for this NDA since metronidazole and tetracycline are not NMEs and bismuth (subsaliylate), metronidazole, and tetracycline have been used in combination for the same indication in another NDA application (Helidac NDA 50-719). All three compounds have well-characterized safety profiles. In addition, no discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.

D. Evaluation of Financial Disclosure

Financial disclosure information was obtained from each investigator. From the available information, none of the investigators in the North American trial reported any significant equity interest.

**Appears This Way
On Original**

VI. Integrated Summary of Efficacy (ISE)

A. Brief Statement of Efficacy Conclusions

The applicant conducted one pivotal trial in North America (HPST99-CUS01) which documents the efficacy of Helizide therapy plus omeprazole (OBMT) compared to an FDA-approved active control regimen of omeprazole, amoxicillin and clarithromycin (OAC).

The results of the supportive data provide further evidence of the efficacy of OBMT therapy in eradication of *H. pylori*.

B. General Approach to Efficacy Review

Only the pivotal North American Phase III trial (HPST99-CUS01) was reviewed in detail. A synopsis is provide below and the complete clinical/statistical review can be found in Appendix 4. The International trial was not reviewed in detail, due to differences in the patient population compared to the North American trial and lack of a comparator arm, but is also summarized below.

Other supportive efficacy data or findings summarized in this section include:

- Pilot studies (2)
- Investigator sponsored studied (4)
- The Agency's finding of safety and efficacy for Helidac® therapy
- Literature review of the contribution of each drug in the OBMT regimen to efficacy

*Clinical Reviewer's Comment: For combination therapy, the regulations require documentation of the contribution of each component to the overall efficacy of the regimen. Helidac and Helizide both contain bismuth, metronidazole, and tetracycline (BMT). Helidac has previously demonstrated the contribution of each component to the efficacy of the overall regimen. Although, Helizide contains biscalcitrates potassium, an NME and a different bismuth salt from what is found in Helidac, there is no clinical difference between the effect of biscalcitrates and other bismuth salts on *H. pylori*. Therefore, we can rely upon the Agency's finding of safety and efficacy for Helidac to provide supportive information for Helizide. In addition, the reviewer has included additional literature data as background information to support the rationale for using BMT combination therapy to treat *H. pylori* and to demonstrate the contribution of each component to the efficacy of the Helizide regimen.*

- Literature review of the efficacy of OBMT therapy

Note: Tables in the ISE have been created by the reviewers, unless otherwise noted.

C. Synopsis of Phase III Efficacy Results

1. North American Trial (HPST99-CUS01)

Title

Efficacy and Safety of Quadruple Therapy by Single-Triple Capsules of Bismaltrate, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *H. pylori*: A Comparison to Omeprazole + Amoxicillin + Clarithromycin (HPST99-CUS01)

Date of Study Initiation: Sept 17, 1999
(First Patient Randomized)

Date of Study Completion: June 22, 2000
(Last Patient Visit)

Date of Report: August 18, 2001

Published Abstracts: Gut 2000;47 Supp1:A100
Gastroenterol 2001;120(3)Supp1:A580

Study Sites

For this study 51 sites were recruited in the United States and Canada and 39 sites randomized at least one patient.

Objectives

The primary objective of this study is to determine the rate of *H. pylori* eradication following therapy with a capsule (Helizide) containing bismaltrate, metronidazole, and tetracycline, given with omeprazole in *H. pylori* positive patients with current or history of duodenal ulcer(s).

Treatment

Patients were randomized to one of the following two treatment regimens for 10 days.

- Three (3) Helizide capsules four times daily, after meals and at bedtime plus one omeprazole 20 mg capsule twice a day after breakfast and supper (OBMT).
- One (1) clarithromycin 500 mg tablet + 2 amoxicillin 500 mg capsules plus one omeprazole 20 mg capsule twice a day before breakfast and supper (OAC).

Study Design

This is a multi-center, randomized, parallel group, open-label Phase III study of the efficacy and safety of 10-day therapy of Helizide capsules given with omeprazole (OBMT) compared to the FDA-approved regimen of omeprazole, amoxicillin and clarithromycin (OAC) in the eradication of *H. pylori*. Since it is difficult to blind a treatment containing metronidazole (because of the taste) and bismuth (because of the darkening effect on the feces), an open-label trial was considered acceptable. The investigators and patients were aware of the study treatment received, however, the personnel at the central laboratories who evaluated the biopsy specimens and UBTs were blinded to treatment.

A total of 299 patients received study therapy (147 OBMT and 152 OAC). The Modified Intent-to-Treat (MITT) population was comprised of 275 patients (138 OBMT and 137 OAC) and there were 244 patients in the Per Protocol (PP) population (120 OBMT and 124 OAC).

Pre-treatment biopsies of the gastric mucosa were taken to assess the presence of *H. pylori* and susceptibility to metronidazole and clarithromycin. A ¹³C-urea breath test (¹³C-UBT) and rapid urease test were also performed pre-treatment to confirm the presence of *H. pylori*. Eradication was confirmed by two negative UBTs at approximately four weeks (i.e., 28 days) and eight weeks (i.e., 56 days) after the end of study therapy. Patients presenting with a positive ¹³C-UBT at either time point underwent a second endoscopy with biopsies to reassess bacterial susceptibility post-treatment (i.e., emerging resistance) to metronidazole and clarithromycin.

Results

The mean age of the patients is 46.5 years in the OBMT group and 47.9 years in the OAC group. The majority of patients are male (59%), Caucasian (59%), and have a history of an ulcer (72%). Drug compliance (defined as $\geq 75\%$ of capsules taken, based on the number returned) is 89.8% and 93.4% for OBMT and OAC, respectively, in the safety population.

Overall Eradication

The *H. pylori* eradication rates at 8 weeks post-treatment (i.e., Day 56), are displayed for the applicant's Modified Intention-to-Treat (MITT) and Per Protocol (PP) analyses in Table 6. The reviewers are in general agreement with the applicant's results.

Clinical and Statistical Reviewers' Comment: Two patients in the OAC group were excluded from the PP population by the applicant due to adverse events apparently related to study medication. The reviewers have included these patients in the PP population as failures. The table below has been modified to reflect this change.

TABLE 6
***H. pylori* Eradication at Day 56 Visit**
Per Protocol and Modified Intent-to-Treat Analyses
(HPST99-CUS01)

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference (OBMT – OAC)
	n/N (%) [95% CI]	N/N (%) [95% CI]	% [95% CI]*
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/126 (85.7) [79.6, 91.8]	6.1 [-0.9, 13.7]
Modified Intent-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

* 95% Confidence Interval for the difference in proportions (OBMT- OAC) is calculated using normal approximation to binomial distribution

The applicant has followed the guidance provided by the Division during the development of Helizide for determining efficacy against *H. pylori*. The following recommendations were made to the applicant regarding establishment of an efficacy threshold.

- Active controlled studies are strongly recommended and should be powered for statistical equivalence or superiority. The investigational regimen will be considered similar to the approved comparator if the lower bound of the 95% two-sided confidence interval for the difference in eradication rates (investigational regimen minus approved active therapy) lies above -15%.
- The sponsor should discuss the choice of comparator regimens well in advance of beginning the study since it is recognized that some FDA approved regimens may be less ideal for comparative trials.

The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Although the delta was not specified in the study protocol, the confidence intervals are above the recommended non-inferiority margin of - 15% and therefore provide evidence of the efficacy of Helizide (OBMT) therapy.

Eradication in Special Populations

Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories were performed by the statistical reviewer to determine whether any of these covariates had a significant effect on *H. pylori* eradication rates. Although the sample size in each strata was small, the results did not indicate that any of these covariates had a statistically significant effect on eradication status.

Eradication by Antimicrobial Susceptibility

Pre-treatment susceptibility to metronidazole and clarithromycin for the MITT and PP populations are shown in Tables 7 and 8 below.

Clinical Reviewer's Comments: The applicant defines metronidazole resistance as a MIC ≥ 8 µg/mL.

Instead, the reviewer has presented the metronidazole data in Tables 7 and 8 using MIC values of ≤ 8 µg/mL and ≥ 16 µg/mL.

TABLE 7
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
MITT Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	MIC ≤ 8µg/mL	MIC ≥ 16µg/mL	Difference (≤ 8 minus ≥ 16) [95% CI]*	Susceptible	Resistant	Difference (Sus. – Res.) [95% CI]*
OBMT	68/74 (91.9)	41/51 (80.4)	11.5 [-0.1, 25.7]	ND	ND	ND
OAC	ND	ND	ND	93/101 (92.1)	3/14 (21.4)	70.7 [43.7, 85.4]

ND = not done

* 95% Confidence Interval for the difference in proportions (Susceptible - Resistant) is calculated using an exact method.

Clinical and Statistical Reviewers' Comment: The difference in eradication rates in the OBMT group between isolates with a metronidazole MIC $\leq 8 \mu\text{g/mL}$ and $\geq 16 \mu\text{g/mL}$ in the MITT population was calculated by the reviewers and found to be 11.5%. The 95% confidence interval for the difference in eradication rates includes zero and suggests that for OBMT treated patients, the rate of eradication in patients is similar whether the isolate has a metronidazole MIC of $\leq 8 \mu\text{g/mL}$ or $\geq 16 \mu\text{g/mL}$.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates was calculated by the reviewers and found to be 70.7%. The 95% confidence interval for the difference in eradication rates does not include zero and affords the conclusion that for OAC treated patients, the rate of eradication in the resistant group is at least 43.7% lower than that of the susceptible group. The difference in eradication rates between susceptible and resistant isolates may be more clinically meaningful for clarithromycin than the difference between isolates with a MIC of $\leq 8 \mu\text{g/mL}$ and $\geq 16 \mu\text{g/mL}$ for metronidazole.

TABLE 8
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
PP Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	MIC $\leq 8 \mu\text{g/mL}$	MIC $\geq 16 \mu\text{g/mL}$	Difference (≤ 8 minus ≥ 16) [95% CI]*	Susceptible	Resistant	Difference (Sus. - Res.) [95% CI]*
OBMT	61/64 (95.3)	38/44 (86.4)	8.9 [-2.0, 23.5]	ND	ND	ND
OAC	ND	ND	ND	88/93 (94.6)	3/13 (23.1)	71.6 [43.6, 87.1]

ND = not done

* 95% Confidence Interval for the difference in proportions (Susceptible - Resistant) is calculated using an exact method.

Clinical and Statistical Reviewers' Comment: The difference in eradication rates in the OBMT group between isolates with a metronidazole MIC $< 8 \mu\text{g/mL}$ and $\geq 8 \mu\text{g/mL}$ in the MITT population was calculated by the reviewers and found to be 8.9%. The 95% confidence interval for the difference in eradication rates includes zero and affords the conclusion that for OBMT treated patients, the rate of eradication in patients is similar whether the isolate has a metronidazole MIC of $\leq 8 \mu\text{g/mL}$ or $\geq 16 \mu\text{g/mL}$.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates calculated by the reviewer and was found to be 71.6%. The 95% confidence interval for the difference in eradication rates does not include zero and affords the conclusion that for OAC treated patients, the rate of eradication in the resistant group is at least 43.6% lower than that of the susceptible group. The difference in eradication rates between susceptible and resistant isolates may be more clinically meaningful for clarithromycin than the difference between isolates with a MIC of $\leq 8 \mu\text{g/mL}$ and $\geq 16 \mu\text{g/mL}$ for metronidazole.

Eradication by Duration of Disease

Eradication rates for patients with active duodenal ulcers compared to those with a history of ulcer disease are shown in Tables 9 and 10 by treatment group for the MITT and PP analyses, respectively.

Clinical Reviewer's Comment: Tables 9 and 10 were adapted by the reviewer from the applicant's original tables. The statistical reviewer recalculated the applicant's confidence intervals using an exact method.

TABLE 9
Eradication Rates (n/N) [95% CI]* by Disease History
MITT Population (HPST99-CUS01)

Treatment	Active Duodenal Ulcer	History of Duodenal Ulcer	
		≤ 2 years ago	> 2 and ≤ 5 years ago
OBMT	100% (15/15) [78.2, 100.0]	85.1% (97 / 114) [77.2, 91.1]	100% (12/12) [73.5, 100.0]
OAC	92.3% (12/13) [64.0, 99.8]	82.8% (96 / 116) [74.6, 89.1]	75% (6/8) [34.9, 96.8]

* 95% Confidence Interval is calculated using an exact method.

TABLE 10
Eradication Rates (n/N) [95% CI]* by Disease History
PP Population (HPST99-CUS01)

Treatment	Active Duodenal ulcer	History of Duodenal Ulcer	
		≤ 2 years ago	> 2 and ≤ 5 years ago
OBMT	100% (14/14) [76.8, 100.0]	90.7% (88/97) [83.1, 95.7]	100% (9/9) [66.4, 100.0]
OAC	91.7% (11/12) [61.5, 99.8]	87.5% (91/104) [90.0, 93.2]	75% (6/8) [34.9, 96.8]

* 95% Confidence Interval is calculated using an exact method.

Rates of Emerging Resistance

Changes in susceptibility to clarithromycin and metronidazole were assessed post-treatment in patients who failed eradication. Unfortunately, many patients refused to have a second endoscopy after treatment. Available results for metronidazole and clarithromycin are presented for the MITT population in Table 11 below.

Statistical Reviewer's Comment: Table 11 should be interpreted with caution as the small number of patients for which data are available most likely do not represent the entire original MITT population.

Clinical Reviewer's Comment: Table 11 was adapted from two of the applicant's tables by the reviewer.

TABLE 11
Baseline *H. pylori* Susceptibility Results vs. Eradication Status After Treatment
MITT Population (HPST99-CUS01)

Susceptibility to Metronidazole at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy			Susceptibility to Clarithromycin at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy		
		R	S	M			R	S	M
Resistant	10	5		5	Resistant	11	8		3
Susceptible	6	1		5	Susceptible	8	1	1	6
Missing	1			1	Missing	4	1		3
Total	17				Total	23			

R = resistant; S = susceptible; M = Missing
 Metronidazole: R ≥ 8 µg/mL; S ≤ 4 µg/mL
 Clarithromycin: R ≥ 1 µg/mL; S ≤ 0.25 µg/mL

Clinical Reviewer's Comment: The applicant defines metronidazole resistance as a MIC ≥ 8 µg/mL.

Instead, the same data can be represented using MIC values as shown in Table 12 below, which was created by the FDA reviewing microbiologist and is consistent with other labels for drugs approved for this indication.

TABLE 12
Metronidazole Susceptibility Test Results and Bacteriological Outcomes^a for HELIZIDE Therapy
(Three HELIZIDE® capsules four times a day plus omeprazole 20 mg twice daily for 10 days)

Metronidazole Pretreatment Results	<i>H. pylori</i> negative (Eradicated)	<i>H. pylori</i> positive (Not Eradicated) Post-treatment susceptibility results		
		MIC ≤ 8	MIC ≥ 16	No MIC
MIC ≤ 8 µg/mL 74	67	0	2	5
MIC ≥ 16 µg/mL 51	42	0	4	5

^a Includes only patients with pretreatment metronidazole susceptibility test results

Conclusions

The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are above the recommended non-inferiority margin of -15% and the *H. pylori* eradication rates for the OBMT treatment provides adequate evidence of efficacy.

2. International Trial - Protocol HPST99-INT01

Title

Efficacy and Safety of Quadruple Therapy by Single Triple Capsules of Bismuth Subcitrate, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *H. pylori*

Date of Study Initiation
(First Patient Enrolled): 03 March 2000

Date of Study Completion
(Last Patient Visit): 25 September 2000

Date of the report: 17 August 2001

Study Sites

This study was conducted in Australia, Europe, and North America. There were 8 study sites.

Objectives

The primary objective of this study was:

- To determine the rate of *H. pylori* eradication following therapy with a single capsule (Helizide) of biscalcitrates, metronidazole, and tetracycline, given with omeprazole, in *H. pylori* positive patients.

Treatment

Helizide 3 capsules four times daily, after meals and at bedtime, plus one omeprazole 20 mg capsules after breakfast and supper (OBMT) for 10 days.

Study Design

This is an open-label, non-comparative, multi-center, Phase III study of the efficacy and safety of 10-day therapy with Helizide capsules given with omeprazole (OBMT) in the eradication of *H. pylori*. A total of 177 patients received study therapy, and 159 patients completed the study. The Modified Intent-to-Treat (MITT) population was comprised of 170 patients, and there were 146 patients in the Per Protocol (PP) population.

The study procedures for documentation of *H. pylori* infection and subsequent eradication were the same as described for the North American trial.

Results

The mean age of the patients is 51 years. Approximately 60% of the patients are male. The majority (> 88%) are Caucasian. Drug compliance (defined as $\geq 75\%$ of medications taken) is 96.84% and 97.72% for the Helizide and omeprazole capsules, respectively, in the MITT population and 98.56% and 99.45%, respectively, in the PP population, based on the number of returned capsules.

The overall eradication rates for OBMT in the PP and MITT analyses are shown in Table 13 below.

TABLE 13
Overall *H. pylori* Eradication at the Day 56 Visit
Per Protocol and Modified Intent-to-Treat Analyses
(HPST99-INT01)

	Per-Protocol n/N (%) [95% CI]*	MITT n/N (%) [95% CI]*
OBMT	142/146 (97.3) [93.1, 99.3]	158/170 (92.9) [88.0, 96.3]

* 95% Confidence Interval is calculated using an exact method.

Eradication rates for OBMT for organisms found to be susceptible or resistant to metronidazole before treatment are shown in Table 14 below.

Clinical Reviewer's Comment:

Instead, the applicant's data are represented in Table 14 using MIC values of $\leq 4 \mu\text{g/mL}$ and $\geq 8 \mu\text{g/mL}$. Of note, the applicant defines metronidazole resistance as a MIC $\geq 8 \mu\text{g/mL}$.

TABLE 14
Eradication Rates (%) by Pre-Treatment Metronidazole Susceptibility
Per Protocol and Modified Intent-to-Treat Analyses
(HPST99-INT01)

	Per-Protocol n/N (%)	MITT n/N (%)
Metronidazole MIC $\leq 4 \mu\text{g/mL}$	75/76 (98.7)	82/86 (95.3)
Metronidazole MIC $\geq 8 \mu\text{g/mL}$	38/40 (95.0)	40/43 (93.0)

Eradication rates for metronidazole isolates with a MIC $\leq 4 \mu\text{g/mL}$ are not significantly different from those with a MIC $\geq 8 \mu\text{g/mL}$ for either the PP or MITT analyses, but are based on a relatively small sample size and may not represent the entire PP or MITT population.

There are 106/170 patients in the MITT population, and 89/146 patients in the PP population with either history or endoscopic confirmation of a duodenal or gastric ulcer or a history of non-ulcer dyspepsia. For the MITT population, eradication rates for patients in the duodenal ulcer, gastric ulcer, and non-ulcer dyspepsia categories are 90.7% (39/43), 100% (14/14), and 93.9% (46/49), respectively. Eradication rates in the PP population were similar or slightly higher, i.e., 94.4% (34/36), 100% (12/12), and 97.6% (40/41) for patients in the duodenal ulcer, gastric ulcer, and non-ulcer dyspepsia categories, respectively. Statistical comparisons show no significant differences in the eradication rates between patients with history or endoscopic confirmation of peptic ulcer (duodenal or gastric ulcer) and history of non-ulcer dyspepsia for either analysis population.

Conclusions

Overall eradication rates for OBMT therapy in the International trial are consistent with, although numerically higher than, the results obtained in the OBMT arm in the North American study for the MITT (92.9% versus 87.7%) and PP (97.3% versus 92.5%) analyses, respectively. These results are similar to other drug therapy trials in which *H. pylori* eradication rates are often higher in European patients than those in North America.

D. Other Supportive Efficacy Data

1. Pilot Studies

In the applicant's initial study (HP93-C01), 57 patients received a treatment with biscalcitrates 120 mg (equivalent to 40 mg Bi₂O₃) + metronidazole 250 mg + tetracycline 500 mg (BMT) administered four times daily one hour before meals and at bedtime for 14 days. The Helizide capsule was not used. All three drugs were dispensed as separate formulations, but packaged together in a blister pack. A control group of 35 patients received matching placebos. Eradication rates in the BMT arm in patients with or without duodenal ulcer(s) or history of duodenal ulcer were 81.5% in the Modified Intention-to-treat (MITT) and 89.8% in the Per Protocol (PP) analysis.

In an effort to increase efficacy, a second trial (HP97-C01) was undertaken with the addition of a proton pump inhibitor (omeprazole) to the BMT regimen. For patient convenience, the treatment duration was reduced from 14 days to 7 days and the tetracycline dose was reduced from 500 mg to 250 mg four times daily. The dose regimen in this study consisted of biscalcitrates 120 mg (equivalent to 40 mg Bi₂O₃) + metronidazole 250 mg + tetracycline 250 mg administered four times daily one hour before meals and at bedtime given with one omeprazole 20 mg tablet one hour before the morning and evening meal. As in the first pilot study, the Helizide capsule was not used. All three drugs were dispensed as separate formulations, but packaged together in a blister pack. One hundred and sixty-one (161) patients with or without duodenal ulcer or history of duodenal ulcer were evaluable by MITT analysis and 146 in the PP analysis. Eradication rates (95% Confidence Interval) were 80% (73.3%-85.7%) and 84% (78.3%-90.2%) for MITT and PP analysis, respectively.

2. Investigator Sponsored Trials

Four studies were also carried out using a prototype to the Helizide capsule by independent investigators. The applicant supplied the study drug(s) to the investigators, but did not contribute to the study design or analysis of results. The prototype capsule contained biscalcitrates (equivalent to Bi₂O₃ 60 mg) + metronidazole 125 mg + tetracycline 125 mg and was administered as two capsules after meals and before bedtime. MITT eradication rates are shown in Table 15 below.

Clinical Reviewer's Comment: The raw data from these trials were not available to the reviewer. The Modified Intention-to-Treat (MITT) analyses reported in the table below were conducted by the applicant. The applicant notes that they have attempted to provide as accurate a summary as possible based on the data available to them, but it is possible that the investigators performed analyses on a slightly different database and therefore the results below may not match those published in the literature.

Table 15 below was adapted from the applicant's table.

TABLE 15
Summary Results of Investigator Sponsored Trials

BMT plus...	Number of patients	MITT eradication rate
No PPI x 10 days ¹	53	50/53 (94.3%)
Lansoprazole 30 mg BID x 7 days ²	66	54/65 (83.1%)
Omeprazole x 7 days ³	65	56/65 (86%)
Pantoprazole 40 mg BID x 7 days ³	33	27/33 (81.8%)

¹de Boer WA, Van Etten RJXM, Schneeberger PM, et al. A single drug for *Helicobacter pylori* infection: First results with a new bismuth triple moncapsule. Am J Gastroenterol 2000;95:641-5.

²de Boer WA, Van Etten RJXM, Van De Wouw BAM, et al. Bismuth-based quadruple therapy for *Helicobacter pylori* – A single triple capsule plus lansoprazole. Aliment Pharmacol Ther 2000;14:85-9.

³unpublished

3. Agency's Finding of Safety and Efficacy for Helidac® Therapy

Included among the supportive information provided by the applicant is the Agency's finding of safety and efficacy for Helidac® therapy. On August 15, 1996 Helidac® therapy was approved in combination with an H₂-receptor antagonist for the treatment of patients with an active duodenal ulcer associated with *H. pylori* infection. Of note, the Helidac NDA was also a literature-based application under FD&C Act Section 505(b)(2).

Helidac therapy consists of bismuth subsalicylate 525 mg (two 262.4 mg chewable tablets), 250 mg metronidazole (one 250 mg tablet), and 500 mg tetracycline (one 500 mg capsule) taken four times daily (at meals and bedtime) for 14 days plus an H₂-receptor antagonist approved for the treatment of acute duodenal ulcer. The bismuth, metronidazole, and tetracycline capsules are packaged together in 14 blister cards, one for each day of therapy. The H₂-receptor antagonist is prescribed separately.

The Helidac approval was based upon of two randomized, controlled trials by Graham et al. (References 1 and 2) and one uncontrolled trial by Cutler et al (Reference 3).

Eradication rates in patients with active duodenal ulcer disease following Helidac therapy plus an H₂-receptor antagonist are shown in Table 16 below and are taken from the Helidac package insert:

Clinical Reviewer's Comment: The table below was modified by the reviewer and the formatting is not identical to the table found in the Helidac package insert (e.g., the footnote numbering has been changed).

TABLE 16
***H. pylori* Eradication Following Use of Helidac Therapy**

Investigator	Eradication Rate in Duodenal Ulcer Patients*	95% Confidence Intervals
Graham ^{1,2}	77% (N = 39)	61% - 89%
Cutler ³	82% (N = 51)	70% - 92%

*Evaluable patients were defined as having a confirmed duodenal ulcer within 2 years prior to treatment and having taken 14 days of bismuth subsalicylate, metronidazole, and tetracycline (range 11 to 17 days). Eradication was defined as no evidence of *H. pylori* infection by culture, rapid urease test and/or urea breath test from at least 4 weeks post-treatment up to 1 year post-treatment.

As seen in the table, the eradication rates in patients with active duodenal ulcers obtained with Helidac therapy plus an H₂-receptor antagonist are lower than those obtained in patients with active or a history of duodenal ulcer disease in the North American study with Helizide plus omeprazole (92.5% in the PP analysis and 87.7% in the MITT analysis).

References

1. Graham DY, Lew GM, Evans DG, et al. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. *Ann Intern Med* 1991;115:266-69.
2. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. *Ann Intern Med* 1992;116:705-8.
3. Cutler AF, Schubert TT. Long-term *Helicobacter pylori* recurrence after successful eradication with triple therapy. *Am J Gastroenterol* 1993;88:1359-61.
4. Published Literature Review - Contribution of Each Drug to Efficacy

The reviewer has included additional literature data as background information to support the rationale for using bismuth, metronidazole, and tetracycline in combination to treat *H. pylori* infection and also to support the contribution of each component to the efficacy of the Helizide regimen.

Bismuth, Metronidazole, and Tetracycline (BMT) Therapy

Bismuth salts exert local effects on the gastroduodenal mucosa, including cytoprotective and ulcer healing properties. In addition bismuth compounds kill *H. pylori* organisms by various mechanisms, including inhibition of protein and cell wall synthesis, membrane function, and ATP synthesis. Adherence of *H. pylori* to surface epithelial cells is also impaired. Bismuth monotherapy is effective at suppression of the organism, but eradication rates are low. Addition of one to two antibiotics increases eradication rates.

In order to determine eradication rates for single versus dual versus triple antimicrobial therapy, a meta-analysis was performed by Chiba et al. Eradication rates were obtained from literature articles published between 1982 and 1990. The contribution of each antimicrobial to eradication can be seen in Table 17 below.

Chiba N, Rao BV, Rademaker JW, et al. Meta-analysis of the efficacy of antibiotic therapy in eradicating Helicobacter pylori. Am J Gastroenterol 1992;87:1716-27.

TABLE 17
Eradication Rates by Bismuth Treatment Regimen

Regimen	Number Eradicated / Number Treated	Eradication Rate (%)
Bismuth Alone	76 / 387	19.6 %
Bismuth + Metronidazole	65 / 118	55.1 %
Bismuth + Metronidazole + Tetracycline	191 / 203	94.1 %

BMT Plus Proton Pump Inhibitor (Omeprazole) Therapy

In the proposed Helizide regimen, bismuth triple therapy is combined with the proton pump inhibitor (PPI) omeprazole. Two published literature articles have attempted to address whether addition of a PPI improves eradication when added to bismuth triple therapy.

- *De Boer W, Driessen W, Jansz A, et al. Effect of acid suppression on efficacy of treatment for Helicobacter pylori infection. Lancet 1995;345:817-20.*

Patients with peptic ulcer disease and biopsy-proven *H. pylori* infection received triple therapy for 7 days (colloidal bismuth subcitrate 120 mg four times daily, metronidazole 500 mg three times daily, and tetracycline 500 mg four times daily). In addition, they were randomly assigned to treatment with omeprazole 20 mg twice daily for 10 days, beginning three days before triple therapy, or placebo. Eradication rates, as assessed by endoscopic methods, are shown in Table 18 below.

TABLE 18
BMT Eradication Rates with or without Addition of a PPI
(De Boer et al 1995)

OBMT n/N (%)	BMT n/N (%)	Difference (OBMT – BMT) % [95% CI]*	p-value
53/54 (98.1%)	45/54 (83.3%)	14.8% [4.4, 27.3]	0.02

* 95% Confidence Interval is calculated using an exact method.

Clinical Reviewer's Comment: The regimens studied in this paper are slightly different than the proposed Helizide plus omeprazole regimen. The OBMT regimen used in this study employed 3 days of pre-treatment with omeprazole prior to initiating BMT therapy and the duration of O plus BMT therapy was only 7 days.

- *Borody TJ, Andrews P, Fracchia G, et al. Omeprazole enhances efficacy of triple therapy in eradicating Helicobacter pylori. Gut 1995;37:477-81.*

Symptomatic dyspeptic patients with biopsy-proven *H. pylori* infection received triple therapy five times a day for 12 days (colloidal bismuth subcitrate 108 mg, metronidazole 200 mg, and tetracycline 250 mg). In addition, they were randomized to either 20 mg of omeprazole twice a day or 40 mg of famotidine at bedtime. Eradication rates, as assessed by endoscopic methods, are shown in Table 19 below.

TABLE 19
BMT Eradication Rates with or without Addition of a PPI
(Borody et al 1995)

OBMT n/N (%)	BMT (plus famotidine) n/N (%)	Difference (OBMT – BMT) %	p-value
122/125 (97.6%)	110/124 (88.7%)	8.9%	0.006

Clinical Reviewer's Comment: The regimens studied in this paper are also slightly different than the proposed Helizide plus omeprazole regimen. The duration of BMT therapy was for 12 days and the BMT regimen also included famotidine. However, it is widely accepted that H₂-receptor antagonists, unlike PPIs, contribute little, if anything, to eradication.

Conclusions from Published Literature Data

The addition of each antimicrobial agent appears to contribute to the overall efficacy of the BMT regimen. Also, addition of a proton pump inhibitor (omeprazole) appears to increase the eradication rate achieved by BMT therapy.

5. Literature Review – Efficacy of OBMT Therapy

Clinical Reviewer's Comment: The following data were obtained from literature publications submitted by the applicant. Table 20 in Appendix 1 was also created by the applicant.

The applicant reviewed 31 literature articles in which OBMT therapy was used with various drug doses and duration of treatment. Table 20 in Appendix 1 summarizes these studies. When limited to studies evaluating a treatment duration of 7 days or more, the results show, by MITT analysis, 2281 patients out of 2654 are cured (mean 85.9%, range 65.5% to 100%). Breakdown by metronidazole susceptibility is reported for some of these studies. Of 173 patients with metronidazole susceptible isolates, a mean of 94.2% (range 89.7% to 97.7%) are cured, compared to 91.9% in the North American trial. Of 89 patients with metronidazole resistant isolates 78.7% (range 41.2% to 100%) are cured, compared to 80.4% in the North American trial. The applicant also points out that there is a trend showing higher eradication rates with higher doses of metronidazole (1.5 to 2 grams per day versus 1 gram per day).

E. Summary of Efficacy

The applicant conducted one pivotal trial in North America (HPST99-CUS01) to document the efficacy of Helizide therapy plus omeprazole (OBMT). It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are above a non-inferiority margin of - 15% and provide evidence of the efficacy of Helizide (OBMT) therapy.

Other findings include:

- Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories indicate that none of these covariates have a statistically or clinically significant effect on eradication status.
- The rate of eradication in patients treated with OBMT having a pre-treatment bacterial isolate with a metronidazole MIC ≤ 8 $\mu\text{g/mL}$ is similar to patients having an isolate with a metronidazole MIC ≥ 16 $\mu\text{g/mL}$ in both the MITT and PP analyses. Conversely, in the OAC group the rate of eradication in patients whose bacterial isolates pre-treatment are resistant to clarithromycin (defined as an MIC ≥ 1 $\mu\text{g/mL}$) is statistically inferior to patients having a susceptible clarithromycin pre-treatment isolate.
- No conclusions can be drawn regarding the rates of emerging resistance to either OBMT or OAC due to the few number of patients with culture results available post-treatment.

The results of the supportive data provide further evidence of the efficacy of Helizide therapy plus omeprazole (OBMT).

- The International trial (HPST99-INT01) demonstrates eradication rates (92.9% by MITT analysis and 97.3% by PP analysis) consistent with, and numerically greater than, the pivotal North American trial (87.7% by MITT analysis and 92.5% by PP analysis)
- Two pilot studies using BMT therapy administered as separate formulations in a blister pack with or without a PPI helped to refine the dosing regimen and treatment duration.
- Four investigator-sponsored trials of Helizide therapy using a prototype Helizide capsule with or without a PPI demonstrate eradication rates similar to what was observed in the Phase III trials.
- The Agency's finding of safety and efficacy for Helidac® therapy (bismuth subsalicylate, metronidazole, tetracycline) plus an H₂-receptor antagonist.
- Literature data demonstrates incremental increases in eradication rates achieved with each component of bismuth triple therapy over bismuth alone (19.6% for bismuth, 55.1% for bismuth plus metronidazole, and 94.1% for bismuth plus metronidazole plus tetracycline). Addition of a proton pump inhibitor (omeprazole) to BMT therapy also increases eradication rates (by 8.9 to 14.8%) over use of BMT alone.
- The published efficacy of OBMT therapy for 7 to 14 days (mean 85.9%, range 65.5% to 100%) is similar to the pivotal North American trial (87.7%) as determined by MITT population analysis.

blank page

VII. Integrated Summary of Safety (ISS)

A. Brief Statement of Safety Conclusions

There are no clinical meaningful differences between OBMT and OAC therapy in the incidence of adverse events (AEs) in the pivotal North American trial. Although the safety data from the International trial are not pooled with the North American trial, the results are supportive of each other with regards to OBMT therapy. The AEs reported for OBMT therapy in both trials do not suggest that patients experience neurotoxicity related to bismuth after exposure to Helizide therapy.

B. Description of Drug Exposure

The safety database for this NDA contains data from two clinical pharmacology studies, one pivotal Phase III trial and one supportive Phase III trial. The number of patients exposed and the duration of exposure is shown in Table 21 below.

The data from each of the four studies included in the database (i.e., two clinical pharmacology studies, one pivotal Phase III trial and one supportive Phase III trial) will be presented separately. Results will not be pooled.

Data from the initial two pilot clinical trials conducted by the applicant, which did not use the Helizide formulation (HP93-C01 and HP97-C01), as well as the four investigator sponsored trials, in which the applicant's role was to provide study drugs to the investigators, will not be discussed.

TABLE 21
Extent of Exposure to Helizide in Clinical Trials
Number of Subjects/Patients per Treatment

Trial		Duration of Treatment	Number of Subjects/Patients
Clin Pharm	HLD-PO-241	3 doses	23
	HLD-PO-180	6 days	36
Phase III	HPST99-CUS01	10 days	147
	HPST99-INT01	10 days	177
TOTAL			383

C. Methods and Specific Findings of Safety Review

Note: Tables in the ISS have been reproduced from the applicant's submission, unless otherwise noted.

The data from each of the four studies included in the database (i.e., two clinical pharmacology studies, one pivotal Phase III trial and one supportive Phase III trial) will be presented separately. Results will not be pooled.

In the safety review special attention was paid to the occurrence of any AE suggesting neurotoxicity. Average steady-state blood concentrations of bismuth above 50 ng/mL are

known to induce a clinical syndrome of bismuth encephalopathy. Symptoms have an insidious onset. The patient first experiences weakness and fatigue followed by confusion, loss of memory, muscle twitching, loss of fine muscle control, and difficulty in walking. Ultimately, patients become bedridden, incontinent and disoriented.

Concentrations of > 50 ng/mL and > 100 ng/mL have been suggested in the literature as "safety" and "alarm" levels, respectively, for bismuth toxicity (see references below). Steady state concentrations of bismuth are reached after 4 to 5 weeks of chronic dosing. The recommended treatment duration of Helizide plus omeprazole therapy is 10 days, therefore, it is unlikely that patients receiving treatment will achieve steady state concentrations of bismuth or experience related toxicity.

In the drug-interaction study (Phase I clinical pharmacology study) conducted by the applicant of Helizide in combination with omeprazole, one subject had a bismuth concentration of > 50 ng/mL, but it did not exceed 100 ng/mL (i.e., 73.2 ng/mL). This concentration was obtained following multiple dosing at the time of maximum (peak) concentration and was transient. There is no clinical evidence in the literature to suggest that transient high peak concentrations are related to toxicity. In addition, steady state concentrations of bismuth are obtained only after 4 to 5 weeks of chronic dosing and the duration of dosing in the drug-interaction study was 6 days. Since the recommended treatment duration is 10 days, it is unlikely that patients receiving Helizide will achieve steady state concentrations of bismuth. Also of note, the drug-interaction study was performed under fasting conditions. Food decreases the systemic absorption of bismuth and Helizide is recommended to be taken after meals.

Clinical Reviewer's Comment: For more information see Clinical Pharmacology and Biopharmaceutics Review by Joette M. Meyer, Pharm.D. filed with this NDA.

Concentrations of bismuth in patients enrolled in the Phase III trials were not obtained. However, the reported adverse events do not suggest that patients experienced neurotoxicity during therapy.

References

1. Slikkerveer A and FA de Wolff. Pharmacokinetics and toxicity of bismuth compounds. *Med Toxicol Adverse Drug Exp* 1989; 4 (5): 303-323.
2. Serfontein WJ and al. Bismuth toxicity in man I. Bismuth blood and urine levels in patients after administration of a bismuth protein complex (Bicitropeptide). *Res Comm Chem Pathol Pharmacol* 1979; 26 (2): 383-389.
3. Serfontein WJ and R. Mekel. Bismuth toxicity in man II. Review of bismuth blood and urine levels in patients after administration of therapeutic bismuth formulations in relation to the problem of bismuth toxicity in man. *Res Comm Chem Pathol Pharmacol* 1979; 26 (2): 391-411.

1. Overview of Adverse Events

North American Trial

In the pivotal trial, an adverse event (AE) was defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment". A

treatment emergent adverse event (TEAE) is defined as any event not present prior to exposure to study medication or any event already present that worsens in either intensity or frequency following exposure to study medication.

Two hundred and ninety-nine (299) patients (147 OBMT + 152 OAC) were exposed to at least one dose of the study drugs and constitute the safety population. Of these patients, 86/147 (58.5%) in the OBMT group and 90/152 (59.2%) in the OAC group reported TEAEs. In the OBMT group there are 212 events reported and 236 events reported in the OAC group. All TEAEs are shown in Table 22 in Appendix 3.

Among the TEAEs, most are classified as mild to moderate in intensity. Only four events are classified as severe in intensity in each group. They are headache, dyspepsia, apnea, and GI bleeding for OBMT and abdominal pain, taste perversion, vaginitis, and hematuria for OAC. The symptom of dyspepsia is rated as possibly related to study drug, taste perversion is rated as certainly related to study drug, and the others are rated as unlikely to be related to study drug.

Two adverse events are classified as serious TEAEs, one death and one hospitalization; neither is deemed to be associated with study drug. These patients are discussed further under the ISS Sections on Death and Non-Fatal Serious Adverse Events.

The most frequent TEAEs (incidence >1%) by treatment group are shown below in Table 23. For both treatments gastrointestinal adverse events are the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality is a relatively common side effect and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). The applicant noted that "stool abnormality" may refer to the darkening effect of bismuth on the stool and that it may have also been under-reported, since the patients were told *a priori* about this effect. Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Clinical Reviewer's Comment: The reviewer evaluated the safety data for possible signs and symptoms of bismuth encephalopathy (e.g., myoclonic jerks, trembling, memory disturbances, confusion and problems of physical coordination) possibly caused by treatment with OBMT, since prolonged exposure to average steady-state blood concentrations of bismuth > 50 ng/mL have been known to cause bismuth neurotoxicity.

Of the patients treated with OBMT the following events occurred: asthenia in 6 patients (4.1%) and amnesia in one patient. Asthenia was also reported in the OAC group in 4 patients (2.6%). Based on these events, and the fact that bismuth concentrations are not at steady state after 10 days of treatment with Helizide, the reviewer concludes that it is unlikely that Helizide treatment causes bismuth-associated encephalopathy.

TABLE 23
Treatment-Emergent Adverse Events [n(%)] by Treatment Group
(Incidence > 1%, by Decreasing Frequency)
Study HPST99-CUS01

Adverse Events by Preferred Term	OBMT (n = 147)	OAC (n = 152)
Stool Abnormality	23 (15.6)	7 (4.6)
Diarrhea	13 (8.8)	23 (15.1)
Dyspepsia	13 (8.8)	17 (11.2)
Abdominal Pain	13 (8.8)	15 (9.9)
Nausea	12 (8.2)	16 (10.5)
Headache	12 (8.2)	11 (7.2)
Flu Syndrome	8 (5.4)	5 (3.3)
Taste Perversion	7 (4.8)	18 (11.8)
Asthenia	6 (4.1)	4 (2.6)
Vaginitis	6 (4.1)	4 (2.6)
Dizziness	5 (3.4)	4 (2.6)
Lab Test Abnormality	4 (2.7)	4 (2.6)
Pain	3 (2.0)	7 (4.6)
Infection	3 (2.0)	5 (3.3)
Pharyngitis	3 (2.0)	4 (2.6)
Pain Back	3 (2.0)	2 (1.3)
SGPT Increased	3 (2.0)	0
Urinary abnormality	3 (2.0)	0
Infection	2 (1.4)	6 (3.9)
Rhinitis	2 (1.4)	4 (2.6)
Dry Mouth	2 (1.4)	1 (0.7)
Vomit	2 (1.4)	1 (0.7)
Anxiety	2 (1.4)	0
Gastritis	2 (1.4)	0
Gastroenteritis	2 (1.4)	0
Pain, Chest	2 (1.4)	0
Palpitation	2 (1.4)	0
Rash (Macular/Papular)	2 (1.4)	0
SGOT Increase	2 (1.4)	0
Flatulence	1 (0.7)	6 (3.9)
Cough	1 (0.7)	3 (2.0)
Rash	1 (0.7)	3 (2.0)
Sinusitis	1 (0.7)	2 (1.3)
Pruritis	0	4 (2.6)
Glossitis	0	2 (1.3)

International Trial

In the international trial, adverse events (AEs) and treatment emergent adverse events (TEAEs) are defined the same as in the North American trial (see above).

One hundred and twenty-nine patients (72.9%) experienced a total of 454 non-serious TEAEs during the study. Most are classified as mild to moderate intensity. All TEAEs are shown in Table 24 in Appendix 4.

There are 12 patients (6.8%) who experienced non-serious TEAEs of severe intensity: three patients with diarrhea (certain (2) and probably/likely), two patients with vomiting (certain and probably/likely), two patients with pain abdominal (both possible), furunculosis (unlikely/unrelated), pyrosis (unlikely/unrelated), hypertonia (unlikely/unrelated), rash (certain), and headache (possible).

There is one patient with four serious TEAEs. Six patients discontinued due to TEAEs.

The incidence of non-serious TEAEs occurring in $\geq 1\%$ of patients in the Safety population is presented in decreasing order of frequency in Table 25 below. Patients are counted only once per preferred term, intensity or relationship category.

Clinical Reviewer's Comment: The reviewer evaluated the safety data for possible signs and symptoms of bismuth encephalopathy (e.g., myoclonic jerks, trembling, memory disturbances, confusion and problems of physical coordination) possibly caused by treatment with OBMT, since prolonged exposure to steady-state blood concentrations of bismuth > 50 ng/mL have been known to cause bismuth neurotoxicity.

Of the patients treated with OBMT the following events occurred: asthenia in 12 patients (6.8%), amnesia in 2 patients (1.1%), general spasm in one patient, and thinking abnormality in one patient. Asthenia was also reported for 4 patients on OAC therapy in the North American study. Based on these events, and the fact that bismuth concentrations are not at steady state after 10 days of treatment with Helizide, the reviewer concludes that it is unlikely that Helizide treatment causes bismuth-associated encephalopathy.

TABLE 25
Most Common (≥ 1% of Patients) Treatment-Emergent Adverse Events in the Safety Population (N=177), Study HPST99-INT01

Preferred term*	Statistic	TEAEs	Related** TEAEs	Severe TEAEs
Total Number of Patients	n (%)	129 (72.9)	118 (66.7%)	12 (6.8)
STOOL ABNORMALITY	n (%)	63 (35.6%)	63 (35.6%)	0
TASTE PERVERSION	n (%)	39 (22.0%)	39 (22.0%)	0
DIARRHEA	n (%)	38 (21.5%)	35 (19.8%)	3 (1.7%)
NAUSEA	n (%)	34 (19.2%)	33 (18.6%)	0
HEADACHE	n (%)	29 (16.4%)	29 (16.4%)	1 (0.6%)
PAIN ABDOMINAL	n (%)	26 (14.7%)	23 (13.0%)	2 (1.1%)
DYSPEPSIA	n (%)	18 (10.2%)	4 (2.3%)	0
DIZZINESS	n (%)	13 (7.3%)	12 (6.8%)	0
SOMNOLENCE	n (%)	13 (7.3%)	13 (7.3%)	1 (0.6%)
ASTHENIA	n (%)	12 (6.8%)	12 (6.8%)	0
VOMITING	n (%)	11 (6.2%)	10 (5.6%)	2 (1.1%)
FLATULENCE	n (%)	9 (5.1%)	8 (4.5%)	0
URINE ABNORMALITY	n (%)	9 (5.1%)	9 (5.1%)	0
RASH	n (%)	8 (4.5%)	7 (4.0%)	1 (0.6%)
DRY MOUTH	n (%)	7 (4.0%)	7 (4.0%)	0
PAIN	n (%)	7 (4.0%)	5 (2.8%)	0
PHARYNGITIS	n (%)	7 (4.0%)	4 (2.3%)	0
SPEECH DISORDER	n (%)	7 (4.0%)	7 (4.0%)	0
ANOREXIA	n (%)	6 (3.4%)	5 (2.8%)	0
SGPT INCREASE	n (%)	5 (2.8%)	4 (2.3%)	1 (0.6%)
CONSTIPATION	n (%)	4 (2.3%)	4 (2.3%)	0
FLU SYNDROME	n (%)	4 (2.3%)	1 (0.6%)	0
INSOMNIA	n (%)	4 (2.3%)	4 (2.3%)	0
ULCER MOUTH	n (%)	4 (2.3%)	4 (2.3%)	0
DEPRESSION	n (%)	3 (1.7%)	2 (1.1%)	0
ERUCTATION	n (%)	3 (1.7%)	3 (1.7%)	1 (0.6%)
PARESTHESIA	n (%)	3 (1.7%)	2 (1.1%)	0
VAGINITIS	n (%)	3 (1.7%)	3 (1.7%)	0
VASODILATATION	n (%)	3 (1.7%)	3 (1.7%)	0
AMNESIA	n (%)	2 (1.1%)	2 (1.1%)	0
ANXIETY	n (%)	2 (1.1%)	2 (1.1%)	0
BRONCHITIS	n (%)	2 (1.1%)	0	0
DISCOLOR TONGUE	n (%)	2 (1.1%)	2 (1.1%)	0
GI DISORDER	n (%)	2 (1.1%)	2 (1.1%)	0
HEMORRHAGE GI	n (%)	2 (1.1%)	2 (1.1%)	0
HYPESTHESIA	n (%)	2 (1.1%)	2 (1.1%)	0
PALPITATION	n (%)	2 (1.1%)	1 (0.6%)	1 (0.6%)
PYROSIS	n (%)	2 (1.1%)	1 (0.6%)	1 (0.6%)
SALIVA INCREASED	n (%)	2 (1.1%)	2 (1.1%)	0

*coded using the COSTART dictionary

**defined as certain, probably/likely, or possible

2. Adverse Events by Relationship to Treatment

North American Trial

Of the 212 TEAEs reported with OBMT, 207 are judged in relation to study drug. In the OAC group, 235/236 are judged in relation to study drug.

Of the 207 events in the OBMT group, 123 are deemed related to study drugs (i.e., certain, probably/likely, or possible) and 84 are deemed unrelated or unassessable. The most frequently (>5%) reported adverse events deemed related are: stool abnormality (15.6%), nausea (8.2%), diarrhea (6.8%), and headache (5.4%).

Of the 235 events in the OAC group, 139 were deemed related to study drugs with OAC and 96 are deemed unrelated or unassessable. The most frequently (> 5%) reported adverse events are diarrhea (13.2%), taste perversion (11.8%), nausea (9.2%), dyspepsia (5.95), and headache (5.3%).

TEAEs by relationship to study therapy are shown in Table 26 in Appendix 3.

International Trial

One hundred and eighteen (118) patients out of 177 (66.7%) in the safety population reported at least one event that is judged to be related to study medication (i.e., certainly, probably/likely, or possibly). There is one event (flu syndrome) in which the relationship to study medication could not be assessed. The most common ($\geq 5\%$) non-serious TEAEs related to study medication are stool abnormality, taste perversion, diarrhea, nausea, headache, pain abdominal, dizziness, somnolence, asthenia, vomiting, flatulence, and urine abnormality.

TEAEs related to study therapy are shown in Table 25 above.

3. Adverse Events by Subgroup (Age, Gender and Ethnicity)

A summary of demographic characteristics for patients in the safety population for the North American (HPST-CUS01) and International (HPST99-INT01) trials is shown in Table 27 below. The treatment groups in the North American trial were generally well balanced with respect to demographic characteristics.

Clinical Reviewer's Comment: Table 27 was created by the reviewer.

TABLE 27
Demographic Characteristics
Studies HPST99-CUS01 and HPST99-INT01

Characteristic		North American Trial [N=299] (HPST99-CUS01)		International Trial [N=177] (HPST99-INT01)
		OBMT [N=147]	OAC [N=152]	OBMT
Age	< 65 years	131	130	153
	≥ 65 years	16	22	24
Gender	Male	90	87	105
	Female	57	65	72
Race	Caucasian	84	92	158
	Black	21	12	6
	Asian	11	4	10
	Other	31	44	3

North American Trial

The most frequently reported adverse events (> 6% incidence overall in either treatment group) by age (< 65 and ≥ 65), gender, and race (Caucasian, Black, Asian, Other) are shown below in Table 28A and 28B.

As seen in Table 28A, females have a higher incidence of diarrhea and headache compared to males. This greater frequency was observed in both the OBMT and OAC treatment groups. There is a slight shift in the incidence per treatment for dyspepsia between males and females. Males have a lower incidence of dyspepsia in the OBMT group (6.7%) compared to the OAC group (11.5%). Females have a higher incidence in the OBMT group (12.3%) compared to the OAC group (10.8%). Also while males and females in the OBMT group have a similar incidence of taste perversion, a higher percentage of females in the OAC group (16.9%) compared to the OBMT group (1.8%) experienced this event. However, these differences are slight and unlikely to result in clinically meaningful differences.

Clinical Reviewer's Comment: Although the actual number of patients with diarrhea is low for males and females (i.e., 6 versus 7) the percentages of male and female patients with diarrhea are more disparate (i.e., 6.7% for males versus 12.3% for females), due to the lower number of females enrolled in the trial. A similar situation occurs in the OAC arm (11 males [12.6%] versus 12 females [18.5%] with diarrhea). This difference between males and females in the incidence of diarrhea is noted by the reviewer and it appears females may be more susceptible to diarrhea caused by antimicrobial agents and/or proton pump inhibitors, than males.

As seen in Table 28B, for the gender and race analyses, the numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn.

TABLE 28A
Number (%) of Patients with Frequently Reported Adverse Events by Gender
Safety Population (N=299)
HPST99-CUS01

Reported Adverse Event	Males		Females	
	OBMT (N=90)	OAC (N=87)	OBMT (N=57)	OAC (N=65)
	Stool Abnormality	14 (15.6%)	3 (3.4%)	9 (15.8%)
Diarrhea	6 (6.7%)	11 (12.6%)	7 (12.3%)	12 (18.5%)
Dyspepsia	6 (6.7%)	10 (11.5%)	7 (12.3%)	7 (10.8%)
Abdominal Pain	8 (8.9%)	9 (10.3%)	5 (8.8%)	6 (9.2%)
Nausea	6 (6.7%)	7 (8.0%)	6 (10.5%)	9 (13.8%)
Headache	6 (6.7%)	5 (5.7%)	6 (10.5%)	6 (9.2%)
Taste Perversion	6 (6.7%)	7 (8.0%)	1 (1.8%)	11 (16.9%)

Appears This Way
 On Original

blank page

TABLE 28B
Number (%) of Patients with Frequently Reported Adverse Events by Age and Race Subgroups
Safety Population (N=299)
HPST99-CUS01

Reported Adverse Event	Age < 65		Age ≥ 65		Caucasian		Black		Asian		Other races	
	OBMT (N=131)	OAC (N=130)	OBMT (N=16)	OAC (N=22)	OBMT (N=84)	OAC (N=92)	OBMT (N=21)	OAC (N=12)	OBMT (N=11)	OAC (N=4)	OBMT (N=31)	OAC (N=44)
Stool Abnormality	22 (16.8%)	3 (2.3%)	1 (6.3%)	4 (18.2%)	18 (21.4%)	6 (6.5%)	3 (14.3%)	1 (8.3%)	1 (9.1%)	--	1 (3.2%)	--
Diarrhea	11 (8.4%)	20 (15.4%)	2 (12.5%)	3 (13.6%)	8 (9.5%)	19 (20.7%)	4 (19%)	19 (20.7%)	--	--	1 (3.2%)	2 (4.5%)
Dyspepsia	13 (9.9%)	16 (12.3%)	0	1 (4.5%)	10 (11.9%)	9 (9.8%)	2 (9.5%)	9 (9.8%)	1 (9.1%)	1 (25%)	--	5 (11.4%)
Abdominal Pain	13 (9.9%)	14 (10.8%)	1 (6.3%)	--	9 (10.7%)	8 (8.7%)	1 (4.8%)	1 (4.8%)	--	1 (25%)	3 (9.7%)	5 (11.4%)
Nausea	11 (8.4%)	14 (10.8%)	1 (6.3%)	2 (9.1%)	7 (8.3%)	8 (8.7%)	3 (14.3%)	3 (14.3%)	--	--	2 (6.5%)	7 (15.9%)
Headache	10 (7.6%)	11 (8.5%)	2 (12.5%)	--	6 (7.1%)	5 (5.4%)	2 (9.5%)	2 (9.5%)	3 (27.3%)	1 (25%)	1 (3.2%)	5 (11.4%)
Taste Perversion	5 (3.8%)	17 (13.1%)	2 (12.5%)	1 (4.5%)	4 (4.8%)	16 (17.4%)	2 (9.5%)	--	1 (9.1%)	1 (25%)	--	1 (2.3%)

International Trial

The most frequently reported adverse events (>10% incidence overall) by age (< 65 and ≥ 65), gender, and race (Caucasian, Black, Asian, Other) are shown below in Table 29.

As seen in Table 29, females have a higher incidence of diarrhea, nausea, headache, and taste perversion compared to males. Males have a higher incidence of dyspepsia compared to females. Although the lack of a control group makes interpretation of these events difficult, the differences are slight and unlikely to result in clinically meaningful differences.

For the gender and race analyses, also seen in Table 29, the numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn.

**Appears This Way
On Original**

TABLE 29
Number (%) of Patients with Frequently Reported Adverse Events by Gender, Age and Race Subgroups
OBMT Safety Population (N=177)
HPST99-INT01

Reported Adverse Event	Males	Females	Age < 65	Age ≥ 65	Caucasian	Black	Asian	Other races
	N=105	N=72	N=153	N=24	N=158	N=6	N=10	N=3
Stool Abnormality	37 (35.2%)	26 (36.1%)	54 (35.5%)	9 (37.5%)	54 (34.2%)	2 (33.3%)	4 (40.0%)	3 (100%)
Diarrhea	16 (15.2%)	22 (30.6%)	30 (19.6%)	8 (33.3%)	36 (22.8%)	1 (16.7%)	--	1 (33.3%)
Dyspepsia	13 (12.4%)	5 (6.9%)	16 (10.5%)	2 (8.3%)	18 (11.4%)	--	--	--
Abdominal Pain	15 (14.3%)	11 (15.3%)	20 (13.1%)	6 (25.0%)	23 (14.6%)	1 (16.7%)	1 (10.0%)	1 (33.3%)
Nausea	17 (16.2%)	17 (23.6%)	26 (17.0%)	8 (33.3%)	32 (20.3%)	1 (16.7%)	1 (10.0%)	--
Headache	9 (8.6%)	20 (27.8%)	25 (16.3%)	4 (16.7%)	25 (15.8%)	1 (16.7%)	3 (30.0%)	--
Taste Perversion	17 (16.2%)	22 (30.6%)	31 (20.3%)	8 (33.3%)	31 (19.6%)	2 (33.3%)	4 (40.0%)	2 (66.7%)

Summary of Subgroup Analyses

The results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also have a higher incidence of nausea and taste perversion. Overall, these differences are slight and unlikely to result in clinically meaningful differences.

The numbers of patients in the categories of age > 65 years and Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly and between the various racial subgroups.

4. Discontinuations from Study Due to Adverse Events

North American Trial

One patient discontinued from the study due to a TEAE. Patient # 5242 withdrew from study after one day of OAC treatment because of mild nausea and pruritus.

- Patient #5242, a 39-year-old male, started treatment with OAC on January 6, 2000. On the same day he developed mild nausea and pruritus. The investigator suspected hypersensitivity to drugs and stopped the treatment. The events resolved in one day without any intervening therapy.

International Trial

There are six patients who discontinued drug therapy due to adverse events, as seen in Table 30 below. Two of these patients experienced events that are judged as certainly related to study medication. Patient #502 was advised to discontinue study treatment after eight days because of a generalized skin eruption (rash) all over her body and Patient #507 stopped her medication after two days because she experienced vomiting.

Clinical Reviewer's Comment: The table below was adapted by the reviewer from a similar table created by the applicant.

Appears This Way
On Original

TABLE 30
List of Patients Discontinued from Study Treatment Due to Adverse Events
(HPST99-INT01)

Patient #	Preferred Term*	Duration (Days)	Intensity	Relationship to Study Therapy**	Resolution? (Yes/No)	
112	Paresthesia	1	Mild	Possible	Yes	
	Vomiting	2	Severe	Probably/Likely	Yes	
	Diarrhea	3	Severe	Probably/Likely	Yes	
121	Dizziness	3	Moderate	Possible	Yes	
126	Dizziness	2	Moderate	Probably/Likely	Yes	
	Nausea	2	Moderate	Probably/Likely	Yes	
	Headache	2	Moderate	Possible	Yes	
325	Vomiting	6	Moderate	Possible	Yes	
	Diarrhea	7	Severe	Certain	Yes	
	Anorexia	4	Moderate	Possible	Yes	
	Headache	2	Moderate	Possible	Yes	
502	Headache	11	Moderate	Probably/Likely	Yes	
	Insomnia	11	Moderate	Probably/Likely	Yes	
	Stomatitis	12	Moderate	Certain	Yes	
	Asthenia	17	Moderate	Certain	Yes	
	Anorexia	11	Moderate	Possible	Yes	
	Nausea	11	Moderate	Certain	Yes	
	Stool abnormality	11	Moderate	Certain	Yes	
	Urine abnormality	11	Moderate	Certain	Yes	
	Amnesia	36	Mild	Probably/Likely	Yes	
	Diarrhea	8	Severe	Certain	Yes	
	Rash	5	Severe	Certain	Yes	
	507	Headache	-	Moderate	Probably/Likely	No
		Stool abnormality	2	Mild	Certain	Yes
Taste perversion		2	Mild	Certain	Yes	
Vomiting		2	Severe	Certain	Yes	
Diarrhea		1	Mild	Certain	Yes	
Asthenia		-	Moderate	Certain	No	
Flatulence		-	Moderate	Certain	No	
Pain abdominal		-	Moderate	Certain	No	

*coded using the COSTART dictionary

**defined as certain, probably/likely, possible, or unlikely/unrelated

There are two patients who temporarily interrupted (i.e., stopped and restarted) study medication due to non-serious TEAEs. Patient #418 experienced vomiting of moderate intensity on the same day when she experienced the serious AEs (noted below in the section on Non-fatal Serious Adverse Events). The event is judged as possibly related to study medication, which was temporarily interrupted due to the event. Patient #434 experienced nausea, tachycardia, and anxiety of moderate intensity. The events are

probably/likely related to study medication, which was temporarily interrupted due to these events. These AEs were not reported to recur upon restarting the medication in either patient.

5. Deaths

One patient died in the course of the clinical development program 12 days after completing treatment in the North American trial (HPST99-CUS01).

- Patient #807, a 75-year old man with history of lung cancer, was randomized into the trial in December 1999 in New Brunswick, Canada. He was treated with OBMT from December 8 to 17, 1999. On [REDACTED] he came to the emergency room complaining of shortness of breath. He was found to have pneumonia in the left upper and lower lobes of the lung, and atelectasis of the right upper lobe. He was also diagnosed with atrial fibrillation and pulmonary edema. He was intubated and transferred to ICU. The patient remained in the ICU until [REDACTED] and was then transferred to a hospital floor. His condition deteriorated and he was transferred back to the ICU. The patient died on [REDACTED]. The cause of death was listed as respiratory failure secondary to pneumonia and pulmonary fibrosis. The investigator judged the patient's death as unlikely to be related to study medication.

Clinical Reviewer's Comment: Agree with the investigators' assessment. It is unlikely that this patient's death was related to study drug.

6. Non-Fatal Serious Adverse Events

North American Trial

There was one patient in the OBMT group (#4804) that experienced a non-fatal serious AE.

- Patient #4804, a 66-year old man with an active duodenal ulcer, was randomized into the trial in California. He was treated with OBMT from October 14 to 23, 1999. A post-treatment ¹³C-UBT on November 22, 1999 was negative. On [REDACTED] 1999 he came to the emergency room and a diagnosis of a GI bleed was made. He was hospitalized and treated with omeprazole and famotidine. He recovered and was discharged from the hospital on [REDACTED]. he was re-admitted to the hospital due to a near syncopal episode. He was treated for pneumonia and bronchitis with amoxicillin and discharged on [REDACTED]. A second ¹³C-UBT on January 6, 2000 was also negative. The investigator judged the events as unlikely to be related to study medication.

International Trial

One patient (#418), a 37-year old female experienced a total of four serious adverse events (anxiety, hyperventilation, nausea, and pain abdominal) on the fourth day of the treatment regimen. She was admitted to the hospital complaining of worsening nausea, abdominal pain, dry retching, with associated anxiety and hyperventilation. The patient had a history of depression and anxiety for which she had been prescribed citalopram and oxazepam (prn). She also had a history of abdominal pain, dry retching and nausea since an umbilical surgery 4 months earlier. The patient was kept in the hospital overnight for observation and released the next day. The events resolved after treatment with prochlorperazine and

hyoscine. She temporarily interrupted study medication for two days but resumed medication the day following discharge from the hospital and completed the study. All four events are of moderate intensity, and possibly related to study medication.

Clinical Reviewer's Comment: This patient had a history of anxiety and nausea. Treatment with OBMT may have worsened her pre-existing condition. Therefore, the reviewer agrees with the investigator's assessment that the events were possibly related to study medication.

7. Pregnancy

No patient became pregnant, as evidenced by negative pre- and post-therapy pregnancy tests, while receiving study medication in either the North American or International trials.

8. Clinical Laboratory Evaluations

North American Trial

Laboratory tests for hematology, serum chemistry and urinalysis were performed at baseline and at the end of the study (i.e., between 29 and 35 days after the end of treatment).

Patients in both treatment groups experience increases in ALT and AST levels. When individual patient data are reviewed, however, only three patients are considered to have clinical significant findings, as per the applicant's definition, in the OBMT group while no patient is considered to have a clinically significant finding, per the applicant, in the OAC group.

- Patient #201 presented for an end of study visit (four weeks after having taken the last study medication) and reported having had an episode of nausea, vomiting, and dizziness. Laboratory results showed elevated transaminases (ALT 96 U/L, normal range 0-40; AST 68 U/L, normal range 0-38). An immediate repeat of these tests confirmed the elevations (ALT, 160; AST, 85). No intervening therapy was prescribed. Two months later ALT was 72 U/L and AST was 39 U/L. The condition was considered resolved.
- Patient #1112 presented with a mild increase in ALT at the end of study visit (four weeks after having taken the last study medication). ALT was 107 U/L from a baseline of 41 U/L (normal range, 0-40 U/L). With no intervening therapy, the test was repeated in one week and the ALT was 64 U/L. The condition was considered resolved.
- Patient #3409 presented with a mild increase in ALT at the end of study visit (four weeks after having taken the last study medication). The ALT was 86 U/L, up from a baseline of 46 U/L (normal range, 0-40 U/L). With no intervening therapy, the test was repeated in two weeks and the ALT was 62 U/L. The condition was considered resolved.

No other clinically relevant trends in laboratory tests were observed.

Clinical Reviewer's Comment: The reviewer agrees with the applicant's assessments. Only one of the three OBMT patients had clinical symptoms associated with the abnormal laboratory findings. The clinical consequences of the elevations in the other two patients is not clear.

The occurrence of all three patients with abnormal AST and/or ALT levels in the OBMT group and none in the OAC group is noted. Six patients treated with OBMT in the International trial (see below) also experienced increases in AST and/or ALT. No patient with an increase in AST/ALT was reported to have an increase in bilirubin in the International trial (data not available for the US trial). The cause of these increases is unknown. Each of the components of OBMT was assessed by the reviewer in turn for a possible association with these abnormalities:

- Omeprazole is known to cause increases in AST/SLT levels, but it was a component of both the OMBT and OAC treatment regimens and no patient in the OAC group has an abnormal level reported.*
- Biskalcitrate, and other bismuth salts, are not known to adversely effect the liver. In pharmacology studies done with biskalcitrate to support this submission, no histopathologic changes were noted in the livers of treated animals.*
- Metronidazole is known to interfere with the assays of AST/ALT, but may produce values of zero.*
- Tetracycline is known to cause increases in AST/ALT and in rare cases hepatotoxicity. The dose of tetracycline in the Helizide regimen is within the usual 1 to 2 gram daily dose used for other approved indications.*

From the available data it can not be determined the cause of the increased levels in AST/ALT. The sponsor will be asked to review their post-marketing safety database for Helizide in Canada (approved since March 2003) and at the time of resubmission to the FDA provide information on any liver function test abnormalities reported in Canada.

International Trial

Laboratory tests for hematology, serum chemistry and urinalysis were performed at baseline and at the end of treatment (within four days following completion of therapy).

As shown in Table 31, there are six patients with ALT values $\geq 3 \times$ ULN. Of these patients, four (#330, 409, 423, and 708) have elevated ALT values at baseline which further increased by the end of the 10-day treatment period. The remaining two patients (#120 and 435) had normal liver function tests at baseline. The elevated ALT at the end of treatment visit is reported as a non-serious AE for one patient (Patient #120; possibly related to study drug; no action taken; resolution unknown).

None of the six patients had a corresponding increase in total bilirubin with the increases in AST/ALT.

TABLE 31
Liver Function Tests of Patients with End of Treatment ALT Values ≥ 3 x ULN
(HPST99-INT01)

Patient Number	Test Name	Unit	Result (Pre-Study)	Result (End of Treatment)	Reference Range
120	ALK PHOS	IU/L	94	92	40-120
	ALT	IU/L	34	169*	7-35
	GAMMA GT	IU/L	29	103*	10-55
	TOTAL BILIRUBIN	UMOL/L	7	10	<17
330	ALK PHOS	U/L	33	32	30-90
	ALT	U/L	63*	112*	<35
	AST	U/L	22	47*	<25
	TOTAL BILIRUBIN	UMOL/L	12	12	<17
409	ALK PHOS	U/L	87	77	30-115
	ALT	U/L	68*	124*	5-40
	AST	U/L	55*	62*	5-40
	BILIRUBIN	UMOL/L	6	7	3-21
	GAMMA GT	U/L	48	52	<66
423	ALK PHOS	U/L	88	76	30-115
	ALT	U/L	163*	199*	5-40
	AST	U/L	61*	72*	5-40
	BILIRUBIN	UMOL/L	9	11	3-21
	GAMMA GT	U/L	22	34	<66
435	ALK PHOS	U/L	58	54	30-115
	ALT	U/L	27	120*	5-40
	AST	U/L	21	62*	5-40
	BILIRUBIN	UMOL/L	11	5	3-21
	GAMMA GT	U/L	26	37	<66
708	ALK PHOS	U/L	195*	170*	30-120
	ALT	U/L	41*	128*	<40
	AST	U/L	31	62*	<37
	TOTAL BILIRUBIN	UMOL/L	4	5	<26

* Laboratory value outside the reference range.

No clinically relevant trends in laboratory tests were observed.

9. Vital Sign And Physical Findings Related to Safety

North American Trial

Physical examination findings and vital sign measurements were performed pre-study and at the end of treatment visit. There were no clinically relevant changes, as per the applicant's definition, observed in physical exam findings or vital signs. None of the other changes observed were judged to be related to treatment by the investigator or the applicant.

International Trial

Physical examination findings and vital sign measurements were performed pre-study and at the end of treatment visit. There were no clinically relevant changes, as per the applicant's definition, observed in physical exam findings or vital signs. None of the other changes observed were judged to be related to treatment by the investigator or the applicant.

Clinical Reviewer's Comment: The reviewer agrees with the applicant's assessments.

10. Clinical Pharmacology Studies

In study HLD-PO-241 (a single dose study) there were 23 healthy male subjects included, five of whom did not complete the study. One subject did not return for the first study day (Day 0), three subjects were withdrawn by the investigator for medical reasons, and one subject withdrew consent for personal reasons. There were no withdrawals related to study medication. The number of subjects reporting at least one adverse event by treatment arm are as follows: one in the Helizide fasting group (one AE), 4 in the group receiving the components of Helizide independently (12 AEs), and 7 in the Helizide fed group (9 AEs). Of the AEs judged to be possibly related to treatment, the following occurred more than once across study arms: headache (4 events), increase in ALT (3 events), and dizziness (2 events).

Of the thirty-six (36) healthy male subjects who were included Study HLD-PO-180 (a multiple dose study), thirty-four (34) completed the study. One subject in the Helizide alone arm withdrew consent from the study for personal reasons. One subject in the Helizide + Omeprazole arm was withdrawn due to an adverse event (nausea and vomiting) thought to be related to study drug. The number of subjects reporting at least one adverse event by treatment arm are as follows: 13 in the Helizide alone arm (49 AEs) and 17 in the Helizide + Omeprazole arm (74 AEs). Of the AEs judged to be possibly related to treatment, the following events occurred > 3 times across study arms: headache (12 events), nausea (12 events), abdominal pain (9 events), increase in ALT (9 events), increase in AST (4 events), dizziness (8 events), flatulence (5 events), dyspepsia (5 events), and loose discolored stools (4 events).

Clinical Reviewer's Comment: For a complete description of the design of these studies, see the Clinical Pharmacology and Biopharmaceutics review.

D. Summary of Safety

- In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any AE. For both treatments gastrointestinal AEs are the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache was frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality is a common side effect and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). The applicant noted that "stool abnormality" may refer to the darkening effect of bismuth on the stool and that it may have also been under-reported, since the patients were told *a priori* about this effect. Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8%

versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

- Although the safety data from the International trial are not pooled with the North American trial, the results were supportive of the North American trial for OBMT.
- The AEs reported for OBMT therapy in both the North American and International trials do not suggest that patients experienced bismuth-associated neurotoxicity after exposure to 10 days of treatment with Helizide.
- In both the North American and the International trials, the number of patients who discontinued due to and AE or experienced a non-fatal TEAEs are low. There are no clinically meaningful differences between treatment groups in the rate of discontinuations due to AEs or non-fatal serious AEs in the North American trial. Discontinuations due to AEs most frequently involve the gastrointestinal system or were allergic-type reactions.
- Only one death occurred in the clinical program and is deemed unlikely to be related to study drug.
- Results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also had a higher incidence of nausea and taste perversion. Overall, these differences are slight and unlikely to result in clinically meaningful differences.
- The numbers of patients in the categories of “age > 65 years” or Black, Asian, and other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly and between the various racial subgroups.
- Pediatric patients, patients with renal or hepatic impairment, and pregnant women were specifically excluded from these trials; therefore, it is not possible to comment on the AE profile in these populations. The package insert will reflect the lack of data in these sub-populations.
- In the North American trial, there are no clinically meaningful changes, as per the applicant’s definition, from pre-study to the end of the study visit within or between treatment groups in any of the laboratory parameters analyzed. Both treatment groups appear to experience increases in ALT and AST levels. When individual patient data are reviewed, however, only three patients were considered to have clinical significant findings, per the applicant, in the OBMT group while no patient is considered to have a clinically significant finding, per the applicant, in the OAC group. The clinical relevance of these changes is not known.
- In the International trial, there are no clinically meaningful changes from pre-study to the end of treatment for any of the laboratory parameters analyzed. There are six patients with ALT values $\geq 3 \times$ ULN. The clinical relevance of these changes is not known.

- In the North American and International trials, there are no clinically meaningful changes in any vital sign parameter analyzed.

VIII. Dosing, Regimen, and Administration Issues

The systemic bioavailability of tetracycline is known to be decreased when administered concomitantly with food, milk or cations (e.g., calcium and bismuth salts). However, when bismuth triple therapy is administered for the purposes of *H. pylori* eradication, no provision is made to separate dosing of these two components from each other or from food. Helizide therapy in the current submission was studied in patients instructed to take the Helizide capsule containing the combination of biscaltrate, tetracycline and metronidazole after meals and at bedtime. In the package insert for Helidac® therapy it also states that the bismuth subsalicylate tablets, tetracycline capsules, and metronidazole tablets should be taken with meals and at bedtime.

Co-administration of tetracycline with food or milk results in binding of the drug to macromolecules found in these substances and results in decreased absorption. Co-administration of tetracycline and cations, including bismuth salts, results in chelation of the two drugs into large complex macromolecules that also are not readily absorbed.

The effect of chelation on anti-*H. pylori* activity has not been well studied. It may be that an interaction between tetracycline and bismuth is beneficial, rather than deleterious, when these two drugs are used in combination for the indication of *H. pylori* eradication, as it may contribute to high intraluminal concentrations in the stomach rather than in the systemic circulation. In a meta-analysis by Chiba et al. (*Am J Gastroenterol* 1992;87:1716-27) the eradication rate for bismuth triple therapy is reported as 94.1% compared to 55.1% for bismuth/metronidazole therapy. Although the studies included in this analysis contain little information describing how tetracycline was administered in relation to bismuth, it is unlikely that patients would have been successful in attempting to administer medications more than four times per day.

In summary, there are no prospectively designed studies published that compare triple therapy with bismuth, tetracycline and metronidazole to dual therapy with bismuth and metronidazole, nor has there been any study published that compares dosing of triple therapy in the presence or absence of food. However, while concomitant administration of tetracycline and food or bismuth salts, as part of the Helizide regimen, may result in decreased systemic absorption of tetracycline, it does not appear to diminish the antibacterial activity of this combination.

IX. Use in Special Populations

Patients with renal or hepatic impairment, pediatric patients, and pregnant women were excluded from the Helizide development program. Metronidazole is metabolized by the liver to a great extent and should be avoided in patients with hepatic impairment. Tetracycline hydrochloride is labeled as Pregnancy Category D due to retardation of skeletal development and embryotoxicity. Therefore, Helizide will be labeled as contraindicated in pregnant (Pregnancy Category D) or nursing women, pediatric patients (under the age of 12 years), and in patients with renal or hepatic impairment.

A. Efficacy

Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories indicate that none of these covariates have a statistically or clinically significant effect on eradication status.

B. Safety

The results of the subgroup analyses of AEs by gender in both the North American and International trials indicate that female patients have a higher incidence of diarrhea and headache compared to males. In the International trial they also have a higher incidence of nausea. Overall, these differences are slight and unlikely to result in clinically meaningful differences.

The numbers of patients in the categories of "age > 65 years" or Black, Asian, and Other races are small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events between young and elderly and between the various racial subgroups.

X. Conclusions and Recommendations**A. Conclusions**

In this submission, the applicant demonstrates the activity of Helizide capsules containing biscalcitrates potassium, metronidazole, and tetracycline hydrochloride plus omeprazole (Prilosec) capsules (abbreviated OBMT) in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (active or history). The efficacy of OBMT is compared to a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC regimen is an acceptable comparator since it consistently achieves eradication rates of approximately 70% or greater by Modified Intent-to-Treat (MITT) analysis and 80% or greater by Per Protocol (PP) analysis.

The applicant conducted one pivotal Phase III trial in North America (HPST99-CUS01) to document the efficacy of Helizide therapy plus omeprazole. It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are above a non-inferiority margin of -15% and provide evidence of the efficacy of Helizide plus omeprazole therapy (OBMT) in the treatment of *H. pylori* infection.

Overall eradication rates for OBMT therapy in the non-comparative, supportive Phase III international trial are consistent with, although numerically higher than, the results obtained in the OBMT arm in the North American trial for the MITT (92.9% versus 87.7%) and PP (97.3% versus 92.5%) analyses, respectively. These results are similar to other drug therapy trials in which European rates of *H. pylori* eradication are often higher than those seen in North American trials.

The applicant has also submitted other supportive data and findings to support the efficacy of Helizide. The Agency's finding of safety and efficacy for Helidac® therapy (bismuth subsalicylate, metronidazole, and tetracycline) in combination with an H₂-receptor antagonist

provides supportive information along with literature articles on the efficacy of OBMT therapy.

In the North American trial, there are no clinically meaningful differences between the OBMT and OAC groups in the incidence of any adverse event (AE). For both treatments gastrointestinal AEs were the most commonly reported (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Stool abnormality, presumably due to the darkening effect of bismuth on the stool, is a commonly reported AE and is more common in the OBMT group than the OAC group (15.6% versus 4.6%). Taste perversion is reported in both groups, but more commonly in the OAC group compared to OBMT group (11.8% versus 4.8%). Taste perversion has been described previously in association with both clarithromycin and metronidazole therapy.

Although the safety data from the International trial are not pooled with the North American trial, the results of the International trial are supportive of the North American trial with regard to OBMT. The AEs reported for OBMT therapy in both the North American and International trials do not suggest that patients experience neurotoxicity related to bismuth after exposure to Helizide therapy.

B. Recommendations

Therefore, Helizide capsules (biskalcitrate potassium + metronidazole + tetracycline HCl), when used in combination with omeprazole, are safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. The recommendation is for approval of Helizide given as three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

The applicant received a "not approvable" letter from ODE IV on August 12, 2002 primarily due to deficiencies found by the Office of Compliance upon inspection of the [REDACTED]. The facility was re-inspected on September 8-11, 2003. As a result of the 2003 inspection, the Office of Compliance's overall recommendation is "withhold" due to the continued serious cGMP concerns with [REDACTED] and the biskalcitrate component of the drug product.

Appendix 5 contains the reviewers' proposed changes to the applicant's package insert (dated 9/5/03). It is anticipated that additional labeling discussions will take place prior to approval.

Joette M. Meyer, Pharm.D.
Clinical Reviewer, DSPIDP, ODE IV, CDER

Ruthanna Davi, M.S.
Statistical Reviewer, DB III, CDER

Concurrence:

HFD-590/TLMO/RocaR
HFD-590/TLStat/HigginsK
HFD-590/OfficeDir/CoxE

APPENDIX 1 – LITERATURE TABLE (EFFICACY OF OBMT THERAPY)

blank page

TABLE 20
Efficacy of OBMT Therapy - Summary of the Literature
 DISCUSSION TABLE

REFERENCE	FIRST AUTHOR	DURATION (DAYS)	BI substrate (mg)	T (mg)	M (mg)	O (mg)	# patients cured	# patients entered	MITT %	M sensitive patients cured	M sensitive patients entered	%	M resistant patients cured	M resistant patients entered	%
1 Am J Gastroenterol 1997 Mar;92(3):438-41	KUNG	7	120 qid	500 qid	400 qid	20 bid	50	50	100.0%						
2 Lancet 1995 Apr 1;345(8953):817-20.	DE BOER	7	120 qid	500 qid	500 lid	20 bid	53	54	98.1%						
3 Eur J Gastroenterol Hepatol 1995 Dec;7(12):1189-94.	DE BOER	7	120 qid	500 qid	500 lid	20 bid	37	40	92.5%						
4 Aliment Pharmacol Ther 1997 Feb;11(1):107-8.	VAUTIER	7	120 qid	500 qid	400 5 daily	20 bid	48	52	92.3%	48	52	92.3%	39	39	82.1%
5 Gut 1998 Feb;42(2):166-9.	VAN DER HULST	7	120 qid	500 qid	500 lid	20 bid	74	82	90.2%	42	43	97.7%	32	32	
6 BMJ 1992 Aug 29;305(6852):502-4.	HOSKING	7	120 qid	500 qid	400 qid	not specified	70	78	89.7%						
7 DDW abstracts on CD, New Orleans, 1998.	DEBOER	7	108 qid	500 qid	250 qid	20 bid	33	37	89.2%						
8 Helicobacter 1996;1:145-50.	DE BOER	7	120 qid	500 qid	500 lid	lanso 30 bid	31	35	88.6%						
9 DDW abstracts on disk, Washington, 1997	BOLIN	7	120 qid	500 qid	400 lid	lanso 30 daily	114	130	87.7%						
10 DDW abstracts on disk, San Francisco, 1996	BORODY	7	120 5 daily	250 5 daily	200 5 daily	20 bid	140	161	87.0%						
11 Lancet 1994 Feb 26;343(8896):508-10.	HOSKING	7	120 qid	500 qid	400 qid	20 daily	66	77	85.7%						
12 DDW abstracts on CD, New Orleans, 1998	LAHAIE	7	120 qid	250 qid	250 qid	20 bid	127	161	78.9%	0	0	0.0%	0	0	0.0%
13 J Fam Pract 1996 Dec;43(6):551-5.	GOMOLLON	14	120 qid	500 qid	250 lid	20 daily	25	31	80.6%						
14 DDW abstracts on CD, New Orleans, 1998	CHIBA	7	Subsal 524 bid	500 bid	500 bid	20 bid	21	27	77.8%						
15 Gut 1995 Oct;37(4):477-81.	BORODY	12	120 5 daily	250 5 daily	200 5 daily	20 bid	122	165	73.9%						
16 Aliment Pharmacol Ther 1997;11:935-8.	GRAHAM	10	Subsal 524 bid	500 bid	500 bid	lanso 15 bid	33	46	71.7%	26	29	89.7%	7	17	41.2%
17 DDW abstracts on CD, New Orleans, 1998	GUTIERREZ	14	120 qid	500 qid	500 lid	20 bid	17	24	70.8%						
18 DDW abstracts on CD, New Orleans, 1998	LAHAIE	7	Subsal 524 bid	500 bid	500 bid	20 bid	12	18	66.7%						
19 DDW abstracts on disk, Washington, 1997	MANTZARIS	10	120 qid	500 qid	500 lid	20 bid	38	58	65.5%						
20 Rev Gastroenterol Mex 1988;63(1):21-7	RODRIGUEZ	14	not specified	not specified	not specified	ranitidine	41	59	69.5%						
21 World Congress of Gastroenterology, abstracts on CD, Vienna 1998	GRGOV	14	120 qid	500 qid	50 qid	ranl 500 bid	19	25	76.0%						
22 Helicobacter 1998;3(2):110-4	GOMOLLON	7	120 qid	500 qid	250 lid	20 bid	93	106	87.7%						
23 Helicobacter 1998;3(3):202-5	KORMAN	7	120 qid	500 qid	400 lid	lanso 10 days	198	219	90.4%						
24 Fam Pract 1999;11(5):483-8	LAI	7	not specified	not specified	not specified	lanso	48	51	94.1%						
25 Aliment Pharmacol Ther 2000;14(1):85-9	DEBOER	7	120 qid	250 qid	250 qid	lanso 30 bid	56	65	86.2%						
26 Aliment Pharmacol Ther 2000;14(6):745-50	GRAHAM	14	Subsal 524 lid	500 lid	500 lid	20 daily	24	26	92.3%						
27 DDW abstracts on CD, Orlando, 1999	DEBOER	7	not specified	not specified	not specified	lanso	54	56	96.4%	47	49	95.9%	24	26	92.3%
28 DDW abstracts on CD, Orlando, 1999	KEARNEY	7	subsal	500 qid	250 qid	H2RA	33	38	86.8%						
29 DDW abstracts on CD, Orlando, 1999	KEARNEY	14	subsal	500 qid	250 qid	lanso 30 bid	79	97	81.4%						
30 Med Clin (Barc) 2001;115(1):1-6	GOMOLLON	7	not specified	not specified	not specified	not specified	35	48	72.9%						
31 N Engl J Med 2001;344(13):987-973	CHAN	7	120 qid	500 qid	400 qid	20 daily	369	400	92.3%						
TOTAL							2160	2516	85.9%	163	173	94.2%	70	89	78.7%

**APPENDIX 2 – ADDITIONAL SAFETY TABLES FOR NORTH AMERICAN TRIAL
(HPST99-CUS01)**

blank page

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
Number of Treatment Emergent Adverse Events	n	212	236
Number of Patients with a Treatment Emergent Adverse Event	n (%)	86 (58.5%)	90 (59.2%)
DIARRHEA	n (%)	13 (8.8%)	23 (15.1%)
DYSPEPSIA	n (%)	13 (8.8%)	17 (11.2%)
STOOL ABNORM	n (%)	23 (15.6%)	7 (4.6%)
NAUSEA	n (%)	12 (8.2%)	16 (10.5%)
PAIN ABDO	n (%)	13 (8.8%)	15 (9.9%)
TASTE PERVERS	n (%)	7 (4.8%)	18 (11.8%)
HEADACHE	n (%)	12 (8.2%)	11 (7.2%)
FLU SYND	n (%)	8 (5.4%)	5 (3.3%)
ASTHENIA	n (%)	6 (4.1%)	4 (2.6%)
PAIN	n (%)	3 (2.0%)	7 (4.6%)
VAGINITIS	n (%)	6 (4.1%)	4 (2.6%)
DIZZINESS	n (%)	5 (3.4%)	4 (2.6%)
CONSTIP	n (%)	2 (1.4%)	6 (3.9%)
INFECT	n (%)	3 (2.0%)	5 (3.3%)
LAB TEST ABNORM	n (%)	4 (2.7%)	4 (2.6%)
FLATUL	n (%)	1 (0.7%)	6 (3.9%)
PHARYNGITIS	n (%)	3 (2.0%)	4 (2.6%)
RHINITIS	n (%)	2 (1.4%)	4 (2.6%)
PAIN BACK	n (%)	3 (2.0%)	2 (1.3%)
COUGH INC	n (%)	1 (0.7%)	3 (2.0%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

blank page

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
PRURITUS	n (%)	0	4 (2.6%)
RASH	n (%)	1 (0.7%)	3 (2.0%)
DRY MOUTH	n (%)	2 (1.4%)	1 (0.7%)
SGPT INC	n (%)	3 (2.0%)	0
SINUSITIS	n (%)	1 (0.7%)	2 (1.3%)
URIN ABNORM	n (%)	3 (2.0%)	0
VOMIT	n (%)	2 (1.4%)	1 (0.7%)
ANEMIA	n (%)	1 (0.7%)	1 (0.7%)
ANXIETY	n (%)	2 (1.4%)	0
FEVER	n (%)	2 (1.4%)	1 (0.7%)
GASTRITIS	n (%)	1 (0.7%)	1 (0.7%)
GASTROENTERITIS	n (%)	2 (1.4%)	0
GLOSSITIS	n (%)	2 (1.4%)	0
INFECT URIN TRACT	n (%)	0	2 (1.3%)
MYALGIA	n (%)	1 (0.7%)	1 (0.7%)
PAIN CHEST	n (%)	1 (0.7%)	1 (0.7%)
PALPITAT	n (%)	2 (1.4%)	1 (0.7%)
RASH MAC PAP	n (%)	2 (1.4%)	0
RECTAL DIS	n (%)	2 (1.4%)	0
SGOT INC	n (%)	1 (0.7%)	1 (0.7%)
	n (%)	2 (1.4%)	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
SGPT INC - SGOT INC	n (%)	2 (1.4%)	0
SYNCOPE	n (%)	1 (0.7%)	1 (0.7%)
ABDOMINAL PAIN	n (%)	1 (0.7%)	0
ALLERG REACT	n (%)	0	1 (0.7%)
AMNESIA	n (%)	1 (0.7%)	0
ANEMIA HYPOCHROM	n (%)	0	1 (0.7%)
APNEA	n (%)	1 (0.7%)	0
APPETITE INC	n (%)	1 (0.7%)	0
ARTERIOSCLEROSIS	n (%)	1 (0.7%)	0
ASTHMA	n (%)	1 (0.7%)	0
BILIRUBINEM	n (%)	0	1 (0.7%)
BODY	n (%)	0	1 (0.7%)
BRONCHITIS	n (%)	0	1 (0.7%)
BUN INC	n (%)	1 (0.7%)	0
CREATINE PK INC	n (%)	0	1 (0.7%)
DEHYDRAT	n (%)	1 (0.7%)	0
DEPRESSION	n (%)	1 (0.7%)	0
DUODENITIS	n (%)	1 (0.7%)	0
ENTERITIS	n (%)	1 (0.7%)	0
ERUCTAT	n (%)	0	1 (0.7%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
ESOPHAGITIS	n (%)	1 (0.7%)	0
HEM	n (%)	1 (0.7%)	0
HEM GI	n (%)	1 (0.7%)	0
HEMATURIA	n (%)	0	1 (0.7%)
HERNIA	n (%)	0	1 (0.7%)
HIGH FREQ. BM	n (%)	0	1 (0.7%)
HYESTHESIA	n (%)	0	1 (0.7%)
HYPOGLYCEM	n (%)	0	1 (0.7%)
HYPOTENS	n (%)	1 (0.7%)	0
IMPOTENCE	n (%)	0	1 (0.7%)
INSOMNIA	n (%)	0	1 (0.7%)
LACERATION L MID FINGER	n (%)	1 (0.7%)	0
LIVER FUNC ABNORM	n (%)	0	1 (0.7%)
MALAISE	n (%)	1 (0.7%)	0
MYASTHENIA	n (%)	0	1 (0.7%)
NECK RIGID	n (%)	0	1 (0.7%)
OTITIS EXT	n (%)	0	1 (0.7%)
PAIN BONE	n (%)	0	1 (0.7%)
PAIN EYE	n (%)	1 (0.7%)	0
PAIN HIP	n (%)	0	1 (0.7%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 22
All Treatment Emergent Adverse Events (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
PNEUMONIA BRONCHITIS	n (%)	1 (0.7%)	0
SOMNOLENCE	n (%)	1 (0.7%)	0
SPASM GENERAL	n (%)	0	1 (0.7%)
SURGICAL REPAIR L MENISCUS	n (%)	1 (0.7%)	0
TACHYCARDIA	n (%)	1 (0.7%)	0
TENDER L UPPER QUADRANT	n (%)	0	1 (0.7%)
TESTIS DIS	n (%)	1 (0.7%)	0
ULCER DUODEN	n (%)	1 (0.7%)	0
ULCER STOMACH	n (%)	1 (0.7%)	0
URIN FREQUENCY	n (%)	1 (0.7%)	0
VASO DILAT	n (%)	0	1 (0.7%)
VIRAL URI	n (%)	1 (0.7%)	0
VISION ABNORM	n (%)	1 (0.7%)	0
VOMIT, PAIN ABDO, DYSPEPSIA	n (%)	0	1 (0.7%)
WBC ABNORM	n (%)	0	1 (0.7%)
WEIGHT INC	n (%)	1 (0.7%)	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01)

Preferred Term	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
PNEUMONIA BRONCHITIS	n (%)	1 (0.7%)	0
SOMNOLENCE	n (%)	1 (0.7%)	0
SPASM GENERAL	n (%)	0	1 (0.7%)
SURGICAL REPAIR L MENISCUS	n (%)	1 (0.7%)	0
TACHYCARDIA	n (%)	1 (0.7%)	0
TENDER L UPPER QUADRANT	n (%)	0	1 (0.7%)
TESTIS DIS	n (%)	1 (0.7%)	0
ULCER DUODEN	n (%)	1 (0.7%)	0
ULCER STOMACH	n (%)	1 (0.7%)	0
URIN FREQUENCY	n (%)	1 (0.7%)	0
VASO DILAT	n (%)	0	1 (0.7%)
VIRAL URI	n (%)	1 (0.7%)	0
VISION ABNORM	n (%)	1 (0.7%)	0
VOMIT, PAIN ABDO, DYSPEPSIA	n (%)	0	1 (0.7%)
WBC ABNORM	n (%)	0	1 (0.7%)
WEIGHT INC	n (%)	1 (0.7%)	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT			OAC		
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population	(N=299)						
CONSTIP	n (%)	0	2 (1.4%)	0	1 (0.7%)	5 (3.3%)	0
INFECT	n (%)	2 (1.4%)	1 (0.7%)	0	4 (2.6%)	1 (0.7%)	0
LAB TEST ABNORM	n (%)	1 (0.7%)	3 (2.0%)	0	0	4 (2.6%)	0
FLATUL	n (%)	1 (0.7%)	0	0	2 (1.3%)	4 (2.6%)	0
PHARYNGITIS	n (%)	3 (2.0%)	0	0	4 (2.6%)	0	0
RHINITIS	n (%)	2 (1.4%)	0	0	3 (2.0%)	1 (0.7%)	0
PAIN BACK	n (%)	2 (1.4%)	1 (0.7%)	0	1 (0.7%)	1 (0.7%)	0
COUGH INC	n (%)	1 (0.7%)	0	0	2 (1.3%)	1 (0.7%)	0
PRURITUS	n (%)	0	0	0	0	4 (2.6%)	0
RASH	n (%)	0	1 (0.7%)	0	0	3 (2.0%)	0
DRY MOUTH	n (%)	0	2 (1.4%)	0	0	1 (0.7%)	0
SGPT INC	n (%)	0	2 (1.4%)	0	0	1 (0.7%)	0
SINUSITIS	n (%)	1 (0.7%)	0	0	0	0	0
URIN ABNORM	n (%)	1 (0.7%)	2 (1.4%)	0	2 (1.3%)	0	0
VOMIT	n (%)	1 (0.7%)	2 (1.4%)	0	0	0	0
ANEMIA	n (%)	1 (0.7%)	1 (0.7%)	0	1 (0.7%)	0	0
ANXIETY	n (%)	1 (0.7%)	0	0	0	0	0
FEVER	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
GASTRITIS	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0
GASTROENTERITIS	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin. Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy. Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories. The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'. Adverse events were coded using the COSTART dictionary. Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT			OAC		
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population	(N=299)						
GLOSSITIS	n (%)	0	0	0	0	2 (1.3%)	0
INFECT URIN TRACT	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
MYALGIA	n (%)	0	1 (0.7%)	0	1 (0.7%)	0	0
PAIN CHEST	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0
PALPITAT	n (%)	2 (1.4%)	0	0	0	0	0
RASH MAC PAP	n (%)	0	2 (1.4%)	0	0	0	0
RECTAL DIS	n (%)	0	1 (0.7%)	0	0	1 (0.7%)	0
SGOT INC	n (%)	0	2 (1.4%)	0	0	0	0
SGPT INC - SGOT INC	n (%)	1 (0.7%)	1 (0.7%)	0	0	0	0
SYNCOPE	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
ABDOMINAL PAIN	n (%)	0	1 (0.7%)	0	0	0	0
ALLERG REACT	n (%)	0	0	0	1 (0.7%)	0	0
ANEMIA HYPOCHROM	n (%)	0	0	0	1 (0.7%)	0	0
APNEA	n (%)	1 (0.7%)	0	0	0	0	0
APPETITE INC	n (%)	0	1 (0.7%)	0	0	0	0
ARTERIOSCLEROSIS	n (%)	1 (0.7%)	0	0	0	0	0
ASTHMA	n (%)	0	0	0	1 (0.7%)	0	0
BILIRUBINEM	n (%)	0	0	0	0	1 (0.7%)	0
BODY	n (%)	0	0	0	0	1 (0.7%)	0
BRONCHITIS	n (%)	1 (0.7%)	0	0	0	0	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories.
 The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT			OAC		
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population	(N=299)						
BUN INC	n (%)	0	0	0	0	1 (0.7%)	0
CREATINE PK INC	n (%)	0	1 (0.7%)	0	0	0	0
DEHYDRAT	n (%)	1 (0.7%)	0	0	0	0	0
DEPRESSION	n (%)	1 (0.7%)	0	0	0	0	0
DUODENITIS	n (%)	1 (0.7%)	0	0	0	0	0
ENTERITIS	n (%)	1 (0.7%)	0	0	0	0	0
ERUCTAT	n (%)	0	0	0	0	1 (0.7%)	0
ESOPHAGITIS	n (%)	1 (0.7%)	0	0	0	0	0
HEM	n (%)	0	1 (0.7%)	0	0	0	0
HEM GI	n (%)	1 (0.7%)	0	0	0	0	0
HEMATURIA	n (%)	0	0	0	1 (0.7%)	0	0
HERNIA	n (%)	0	0	0	1 (0.7%)	0	0
HIGH FREQ. BM	n (%)	0	0	0	0	1 (0.7%)	0
HYPSTHESIA	n (%)	0	0	0	1 (0.7%)	0	0
HYPOGLYCEM	n (%)	0	0	0	1 (0.7%)	0	0
HYPOTENS	n (%)	1 (0.7%)	0	0	0	0	0
IMPOTENCE	n (%)	0	0	0	0	0	0
INSOMNIA	n (%)	0	0	0	0	1 (0.7%)	0
LACERATION L MID FINGER	n (%)	1 (0.7%)	0	0	0	1 (0.7%)	0
LIVER FUNC ABNORM	n (%)	0	0	0	1 (0.7%)	0	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.
 Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories.
 The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group					
		OBMT			OAC		
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable
Number of Patients in the Safety Population :	(N=299)						
MALaise	n (%)	0	1 (0.7%)	0	0	0	0
MYASTHENIA	n (%)	0	0	0	1 (0.7%)	0	0
NECK RIGID	n (%)	0	0	0	0	1 (0.7%)	0
OTITIS EXT	n (%)	0	0	0	1 (0.7%)	0	0
PAIN BONE	n (%)	0	0	0	0	1 (0.7%)	0
PAIN EYE	n (%)	1 (0.7%)	0	0	0	0	0
PAIN HIP	n (%)	0	0	0	1 (0.7%)	0	0
PNEUMONIA BRONCHITIS	n (%)	1 (0.7%)	0	0	0	0	0
SOMNOLENCE	n (%)	0	1 (0.7%)	0	0	0	0
SPASM GENERAL	n (%)	0	0	0	0	0	0
SURGICAL REPAIR L	n (%)	1 (0.7%)	0	0	1 (0.7%)	0	0
MENISCUS							
TACHYCARDIA	n (%)	0	1 (0.7%)	0	0	0	0
TENDER L UPPER QUADRANT	n (%)	0	0	0	1 (0.7%)	0	0
TESTIS DIS	n (%)	1 (0.7%)	0	0	0	0	0
ULCER DUODEN	n (%)	0	1 (0.7%)	0	0	0	0
ULCER STOMACH	n (%)	1 (0.7%)	0	0	0	0	0
URIN FREQUENCY	n (%)	1 (0.7%)	0	0	0	0	0
VASO DILAT	n (%)	0	0	0	0	0	0
VIRAL URI	n (%)	1 (0.7%)	0	0	0	1 (0.7%)	0
VISION ABNORM	n (%)	0	1 (0.7%)	0	0	0	0

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin.

Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories.

The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population in each treatment group.

TABLE 26
All Treatment Emergent Adverse Events by Relationship to Study Therapy (HPST99-CUS01) (continued)

Preferred Term	Statistic	Treatment Group							
		OBMT			OAC				
		Unrelated	Related	Unassessable	Unrelated	Related	Unassessable		
Number of Patients in the Safety Population	(N=299)								
VOMIT, PAIN ABDO, DYSPEPSIA	n (%)	0	0	0	0	1 (0.7%)	0		
WBC ABNORM	n (%)	0	0	0	0	1 (0.7%)	0		
WEIGHT INC	n (%)	0	0	1 (0.7%)	0	0	0		

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole; OAC: Omeprazole, Amoxicillin and Clarithromycin. Treatment Emergent adverse events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy. Patients are only counted once within each Preferred Term/relationship, but patients may be presented in more than one relationship categories if the same event occurs within two different relationship categories. The category Related is defined as 'Certain', 'Probably/Likely' and 'Possible'. Adverse events were coded using the COSTART dictionary. Percentages are based on the number of patients in the Safety Population in each treatment group.

**APPENDIX 3 – ADDITIONAL SAFETY TABLES FOR INTERNATIONAL TRIAL
(HPST99-INT01)**

blank page

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01)

Preferred Term	Statistic		OBMT
Number of Patients in the Safety Population	N		177
Number of Treatment Emergent Adverse Events	n		454
Number of Patients with a Treatment Emergent Adverse Event	n (%)		129 (72.9%)
STOOL ABNORM	n (%)		63 (35.6%)
TASTE PERVERS	n (%)		39 (22.0%)
DIARRHEA	n (%)		38 (21.5%)
NAUSEA	n (%)		34 (19.2%)
HEADACHE	n (%)		29 (16.4%)
PAIN ABDO	n (%)		26 (14.7%)
DYSPEPSIA	n (%)		18 (10.2%)
DIZZINESS	n (%)		13 (7.3%)
SOMNOLENCE	n (%)		13 (7.3%)
ASTHENIA	n (%)		12 (6.8%)
VOMIT	n (%)		11 (6.2%)
FLATUL	n (%)		9 (5.1%)
URIN ABNORM	n (%)		9 (5.1%)
RASH	n (%)		8 (4.5%)
DRY MOUTH	n (%)		7 (4.0%)
PAIN	n (%)		7 (4.0%)
PHARYNGITIS	n (%)		7 (4.0%)
SPEECH DIS	n (%)		7 (4.0%)
ANOREXIA	n (%)		6 (3.4%)
SGPT INC	n (%)		5 (2.8%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.
 Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population.

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic		OBMT
	N	n (%)	
Number of Patients in the Safety Population	177		
CONSTIP	4	2.3%	
FLU SYND	4	2.3%	
INSOMNIA	4	2.3%	
ULCER MOUTH	4	2.3%	
DEPRESSION	3	1.7%	
ERUCTAT	3	1.7%	
PARESTHESIA	3	1.7%	
VAGINITIS	3	1.7%	
VASODILAT	3	1.7%	
AMNESIA	2	1.1%	
ANXIETY	2	1.1%	
BRONCHITIS	2	1.1%	
DISCOLOR TONGUE	2	1.1%	
GIDIS	2	1.1%	
HEM GI	2	1.1%	
HYPESTHESIA	2	1.1%	
PALPITAT	2	1.1%	
PYROSIS	2	1.1%	
SALIVA INC	2	1.1%	
ANAL DIS	1	0.6%	

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.
 Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population.

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic	OBMT
Number of Patients in the Safety Population	N	177
ARTHRALGIA	n (%)	1 (0.6%)
BUN INC	n (%)	1 (0.6%)
CONCUSSION	n (%)	1 (0.6%)
DEHYDRAT	n (%)	1 (0.6%)
DERM FUNG	n (%)	1 (0.6%)
DRY EYE	n (%)	1 (0.6%)
DYSURIA	n (%)	1 (0.6%)
ECCHYMOSIS	n (%)	1 (0.6%)
ECZEMA	n (%)	1 (0.6%)
EDEMA PERIPH	n (%)	1 (0.6%)
EDEMA TONGUE	n (%)	1 (0.6%)
EXCESSIVE SUDATION	n (%)	1 (0.6%)
FOOD CRAVINGS	n (%)	1 (0.6%)
FURUNCULOSIS	n (%)	1 (0.6%)
GLOWING CHEEHS	n (%)	1 (0.6%)
GOUT	n (%)	1 (0.6%)
HYPERTONIA	n (%)	1 (0.6%)
ITCHY LEG	n (%)	1 (0.6%)
ITCHY ON FACE	n (%)	1 (0.6%)

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.
 Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy of any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population.

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic		OBMT
	N	n (%)	
Number of Patients in the Safety Population	177		
LEUKORRHEA	1	0.6%	
LIVER FUNC ABNORM	1	0.6%	
PAIN BACK	1	0.6%	
PAIN CHEST SUBSTERN	1	0.6%	
PAIN EYE	1	0.6%	
POST-PRAND. PR FULLNESS	1	0.6%	
PRURITUS	1	0.6%	
PURS AND NEEDLES OVER WHOLE BODY	1	0.6%	
RHINITIS	1	0.6%	
SHOCK	1	0.6%	
SPASM GENERAL	1	0.6%	
STOMATITIS	1	0.6%	
SWEAT	1	0.6%	
TACHYCARDIA	1	0.6%	
THINKING ABNORM	1	0.6%	
THROMBOCYTHEM	1	0.6%	
TONGUE DIS	1	0.6%	
TREMOR	1	0.6%	
ULCER DUODEN	1	0.6%	
URIN FREQUENCY	1	0.6%	

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.

Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.

Patients are only counted once within each Preferred Term.

Adverse events were coded using the COSTART dictionary.

Percentages are based on the number of patients in the Safety Population.

TABLE 24
All Treatment Emergent Adverse Events (HPST99-INT01) (continued)

Preferred Term	Statistic		OBMT
	N	n (%)	
Number of Patients in the Safety Population	177		
VERTIGO		1 (0.6%)	

Notes: OBMT: Bismuth Subcitrate, Metronidazole, Tetracycline and Omeprazole.
 Treatment Emergent Adverse Events are defined as any event not present prior to exposure to study therapy or any event already present that worsens in intensity following exposure to study therapy.
 Patients are only counted once within each Preferred Term.
 Adverse events were coded using the COSTART dictionary.
 Percentages are based on the number of patients in the Safety Population.

APPENDIX 4 – INDIVIDUAL REVIEW OF NORTH AMERICAN TRIAL (HPST99-CUS01)

blank page



I. Clinical and Statistical Review of North American Trial (HPST99-CUS01)

Title

Efficacy and Safety of Quadruple Therapy by Single-Triple Capsules of Biscalcitrates, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *H. pylori*: A Comparison to Omeprazole + Amoxicillin + Clarithromycin (HPST99-CUS01)

Date of Study Initiation: Sept 17, 1999
(First Patient Randomized)

Date of Study Completion: June 22, 2000
(Last Patient Visit)

Date of Report: August 18, 2001

Published Abstracts: Gut 2000;47 Supp1:A100
Gastroenterol 2001;120(3)Supp1:A580

A. Investigators and Study Administrative Structure

There are two principal investigators (PI) for this study: Dr. Loren Laine for the U.S. and Dr. Richard Hunt for Canada. The PIs helped with study design and identification of investigators. Fifty-one (51) sites were recruited and 39 sites randomized at least one patient. Each site had their own investigator and some sites also had co-investigators. All investigators were certified gastroenterologists.

A single central lab () performed all biochemistry assays for screening procedures and post-treatment safety assessments.

Two pathologists, Dr. Hala El-Zimaity, at Baylor College of Medicine, Houston, for U.S. and Dr. Bich Nguyen at CHUM-Hôpital St-Luc, Montréal for Canada evaluated all histological samples for the presence of *H. pylori* on biopsy slides.

A single microbiologist, Dr. Michael Osato at Baylor College of Medicine, Houston supervised all *H. pylori* cultures and sensitivity assessments.

A single central lab () performed all ¹³C-UBT with a FDA approved test.

The labs () pathologists (Dr. El-Zimaity and Dr. Nguyen), and microbiologist (Dr. Osato) were blinded to treatment received by patients.

B. Study Objectives

The primary objective of this study is to determine the rate of *H. pylori* eradication following therapy with a single capsule (Helizide) containing triple therapy consisting of biscalcitrates, metronidazole, and tetracycline, given with omeprazole (OBMT) in *H. pylori* positive patients with current or history of duodenal ulcer(s).

The secondary objectives of this trial are:

- To document the effect of resistance of *H. pylori* to metronidazole and clarithromycin on the efficacy of these treatments.
- To compare the Helizide plus omeprazole regimen (OBMT) to the FDA-approved regimen of clarithromycin 500 mg, plus amoxicillin 1 gram, plus omeprazole 20 mg (OAC)
- To assess the safety of these therapeutic regimens with respect to adverse events.
- To document the rate of secondary resistance induced by these treatments.

Clinical Reviewer's Comment: The Division does not _____ For additional discussion, see the Results section on susceptibility.

C. Investigational Plan

This is a multi-center, randomized, active-controlled, open-label, parallel group study.

Clinical Reviewer's Comment: Since it is difficult to blind a treatment containing metronidazole (because of the taste) and bismuth (because of the darkening effect on the feces), the Division agreed with the applicant that a double-blind trial would be difficult to conduct. The investigators and patients were aware of the treatments; however, the personnel at the central laboratories who evaluated the biopsy specimens and UBTs were blinded to treatment.

H. pylori infected patients with one or more endoscopically confirmed duodenal ulcers or a history of duodenal ulcer disease, who met the inclusion criteria, were randomized to one of the following two treatment regimens for 10 days.

- Three (3) Helizide capsules four times daily, after meals and at bedtime plus one omeprazole 20 mg capsule twice a day after breakfast and supper (OBMT).
- One (1) clarithromycin 500 mg tablet plus two amoxicillin 500 mg capsules + 1 omeprazole 20 mg capsule twice a day before breakfast and supper (OAC).

Helizide plus omeprazole treatment (OBMT) was taken after meals, based on the rationale that a prolonged gastric residence time of the drug increases the duration of contact between *H. pylori* and drugs and that may give better eradication rates.

OAC was taken before morning and evening meals, as used in the trials supporting approval of OAC treatment in the U.S.

Each patient, regardless of treatment regimen, also received 100 tablets of Al(OH)₃ antacid (Amphojel®) as rescue medication. These tablets contained 300 mg of Al(OH)₃ and were taken as 2 tablets as needed, a maximum of 4 times daily.

Patients self-administered the study drugs and were instructed not to take the study medications with milk, other dairy products, or antacids.

The following warnings were made to all patients regardless of their treatment:

- The antacid rescue medication should be taken at least one hour before or two hours after the study medications, since aluminum-, magnesium- or calcium-containing antacids can bind to tetracyclines and interfere with their absorption.
- There is a risk of a disulfiram-like reaction with the combination of alcohol and metronidazole. Therefore, refrain from consuming alcohol during the 10-day treatment period and for the 48 hours following the last dose.
- Women using oral contraceptives: There is a potential decrease in the efficacy of oral contraceptives when used concomitantly with tetracycline (and potentially with other antibiotics). An additional mean of contraception (e.g. condom) is recommended for the rest of the current cycle.
- Avoid exposure to direct sunlight and/or ultraviolet light during the 10-day treatment period and for the 48 hours following the last dose, due to the fact that photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracycline.
- Cisapride, pimozide, and terfenadine are prohibited during the 10- day treatment and for 48 hours following the last dose, due to a potentially dangerous interaction with clarithromycin.

D. Schedule of Visits

Pre-Study Visit(s) (Days –30 to 0)

Upon confirmation of willingness to participate and signature of the informed consent form, each subject began the screening process. Depending on the site's usual procedures, screening assessments could be performed in different order and in one, two, or three visits.

Ideally, at the first visit, after signature of the informed consent form, the patient underwent a ^{13}C -urea breath test (^{13}C -UBT). Collection of medical history and demographic data, complete physical examination, routine hematology, clinical chemistry, urinalysis, and pregnancy test, if indicated, were also done. If the result of the ^{13}C -UBT was positive, the patient could be rescheduled for another Pre-Study visit. A history of duodenal ulcer(s) must be adequately documented by reports from previous endoscopies/X-rays or the presence of an active duodenal ulcer must be documented from the study endoscopy.

Upon confirmation of presence of *H. pylori* by the ^{13}C -UBT (about 24 hours after the test), the investigator performed an endoscopy and took 6 biopsies. One antrum biopsy was used for rapid urease test to provide an immediate result as to the presence of *H. pylori*. Three biopsies, two from antrum and one from corpus, were used for histology and two others, one from antrum and one from corpus, for assessment of resistance of *H. pylori* to metronidazole, clarithromycin, amoxicillin, and tetracycline. If the rapid urease test was positive, the patient was assigned a treatment number, in sequential order for the site, and was allowed to start the treatment. The rapid urease test result had to be later confirmed by histology and/or culture to validate the admissibility of the patient.

If a patient started medication on the basis of a positive rapid urease test and was later found *H. pylori* negative by both histology and culture or by ^{13}C -UBT alone, he/she was

excluded from the modified intent-to-treat (MITT) and efficacy analyses and was considered for safety analysis only. It was left to the investigator's judgement to continue or to stop the 10-day treatment if it was still on-going.

If needed, for logistic and/or practical reasons, all Pre-Study procedures could be done on the same day. In that case, the results of the ^{13}C -UBT were not available before performing the endoscopy. In order to avoid unnecessary procedures and risks for the patient, the investigator must then perform a serologic test that must be positive for *H. pylori* before undergoing the endoscopy.

Also, if needed for practical reasons (i.e. endoscopy performed at a different site than the follow-up), a third pre-study visit could be done. The pre-study procedures were then as follows: Pre-study Visit part 1: as described above. If the ^{13}C -UBT was positive, the patient was referred for endoscopy. Pre-study Visit part 2: endoscopy with rapid urease test and biopsies were performed at the endoscopic site. If the rapid urease test was positive the patient was sent back to the primary care site. Pre-study Visit part 3: the patient came back to the primary care center for his/her drug supply and to start the study.

Study Day 1 was the day when patient started the medication. Unless contra-indicated, it was recommended that the patient should take his/her first dose in the morning. Study Day 1 should not be more than 7 days apart from confirmation of presence of *H. pylori*.

It was possible to perform the endoscopy first, before the ^{13}C -UBT. In this case, the endoscopy was medically necessary for a reason other than *H. pylori* detection. Ideally, the presence of *H. pylori* in the patient had to be documented before endoscopy by serologic testing.

Following successful pre-study evaluations, patients took the medications for 10 days as instructed. Return visits were scheduled as follows:

End-of-Treatment Visit (Days 11-14)

Within 4 days following completion of therapy (i.e. Study Days 11-14), the physical examination and clinical laboratory (hematology, biochemistry and urinalysis) tests done at pre-study were repeated. A pregnancy test was repeated if it had been done at entry. Adverse events and concomitant medication were recorded. Study medications were retrieved at this visit (except for Amphojel).

End-of-Study Visit (At least Day 38)

Between approximately 29 and 35 days after the end of treatment (i.e. Study Days 39-45), patients returned to the study site for a second ^{13}C -UBT and adverse event assessment. Concomitant medications were also recorded. This visit was scheduled as early as possible but not before 29 days after the end of treatment. Patients who did not complete their 10-day treatment could be scheduled to have a repeat ^{13}C -UBT between approximately 29 and 35 days after the time that they would have completed therapy.

If the result of the ^{13}C -UBT was negative, the patient was scheduled for the Confirmation Visit. If the result was positive, the patient underwent a second endoscopy with 2 biopsies for *H. pylori* culture and susceptibility testing to metronidazole and clarithromycin. This patient did not need to undergo the Confirmation Visit and was treated as deemed appropriate by the investigator, outside the scope of the protocol.

Confirmation Visit (At least Day 56)

Between approximately 56 and 63 days after the end of treatment (i.e. Study Days 66-73), patients returned to the study site for a third ¹³C-UBT and adverse event assessment. Concomitant medications were also recorded. This visit was scheduled as early as possible but not before 56 days after the end of treatment.

E. Inclusion Criteria

- Male or non-pregnant female aged 18 to 75 years inclusively.
- Positive for *H. pylori* by:
 - Both ¹³C-UBT and histology
 - OR
 - Both ¹³C-UBT and culture.
- Current or history (within 5 years) of duodenal ulcer(s) of at least 3 mm documented by endoscopy or radiology.
- Mental and legal ability to give a written informed consent.

F. Exclusion Criteria

- Previous surgery of the stomach such as partial gastrectomy, gastroplasty, or vagotomy. Patients with simple closure of a perforated ulcer or oversewing of a bleeding ulcer may be included.
- Dysphagia or vomiting as major symptoms.
- Any current or recent (within 1 month) hematemesis, melena, or documented gastrointestinal bleeding or iron-deficiency anemia of clinical significance.
- Pregnancy or lactation, or women of childbearing potential not using reliable contraception (i.e., ovariectomy, hysterectomy, tubal ligation for at least 6 months, oral contraceptive, barrier method).
- Inability to abstain from alcohol intake during treatment period.
- Presence of clinically significant impairment of renal function, hepatic function, or liver disease.
- Presence of a contraindication to the use of metronidazole (e.g. active neurological disorder, history of blood dyscrasia, uncorrected hypothyroidism, uncorrected hypoadrenalism, or alcoholism), tetracycline (known sensitivity to tetracyclines), clarithromycin (known hyper-sensitivity to macrolides, use of cisapride, pimozone or terfenadine), amoxicillin (known sensitivity to penicillins), or omeprazole (known sensitivity to omeprazole).
- Presence of other serious medical condition(s) precluding participation.
- Use of antibiotics in the 30 days before enrollment.
- Regular use (> 3 times per week) of bismuth compounds in the 30 days before enrollment.
- Requirement for anticoagulant therapy (except for acetyl-salicylic acid in daily dose of 325 mg or less).
- Use of any experimental drug within the 30 days prior to enrollment.
- Previous attempt with antibiotic treatment to eradicate *H. pylori*.
- Chronic use of anti-ulcer drugs, including H₂ receptor antagonists, sucralfate and prostaglandins during the 1-week period preceding the ¹³C-UBT at enrollment.
- Chronic use of a proton pump inhibitor in the 15 days preceding ¹³C-UBT at entry.

- Patient known to be positive for HIV, hepatitis, or other diseases transmissible by blood or biopsy samples.
- Presence of Zollinger Ellison Syndrome.
- Chronic use of NSAID, except for acetyl-salicylic acid 325 mg or less daily.

Patients were required to discontinue chronic use of PPIs starting at least 15 days prior to enrolment and continuing until the third ¹³C-UBT, done between approximately 56 and 63 days after the end of treatment, except for the omeprazole administered as the study drug. Patients were required to discontinue chronic use of H₂-receptor antagonists starting at least 7 days prior to enrolment and continuing until the third ¹³C-UBT.

In the event that a patient developed a systemic infection (bronchitis, sinusitis, pneumonia, etc.) requiring systemic antibiotic therapy between Study Days 11 and 73, and received antibiotics known to be effective against *H. pylori* (i.e., metronidazole, tetracycline, amoxicillin, clarithromycin, and azithromycin), he/she was excluded from the study. All other antibiotics were evaluated on a case-by-case basis for their known efficacy against *H. pylori*.

Throughout the study, all chronic medications for dyspepsia, including H₂-receptor antagonists, either by prescription or over the counter, proton pump inhibitors, homeopathy and medicinal herbals were prohibited. Antacids, except bismuth-based products, could be used, but only sporadically if severe dyspepsia was experienced, and the dose was kept to a minimum (2 tablets as needed, a maximum of 4 times daily).

G. Patient Removal

Patients were able to discontinue their participation in the study at any time. In addition, the investigators and the applicant were permitted to discontinue a patient from the study due to development of an adverse event, a significant protocol violation, or if the patient required an immediate medical or surgical procedure, which would compromise the patient's continued participation.

H. Other Study Design Features

The study procedures and evaluations were developed in compliance with the guidelines current at that time (1999) whenever possible:

- DAIDP. Guidance for Industry - Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products. Indication 25: *H. pylori* (FDA, 1997: draft).
- Points to Consider when Reviewing Therapeutic Regimens for Eradication of *H. pylori* in GI disease (Health Canada: draft).
- Guidelines for Clinical Trials in *H. pylori* Infection (European *H. pylori* Study Group).
- Canadian *H. pylori* Consensus Conference, Guidelines for the Management of *H. pylori* Infections (American College of Gastroenterology).

I. Diagnostic Methods

¹³C-UBT

Presence or absence of *H. pylori* was assessed by ¹³C-UBT, analyzed at a central lab

Biopsies of Gastric Mucosa

At screening, 6 separate biopsies were taken: 4 from the antrum (1 from the lesser curvature and 3 from the greater curvature) and 2 from the body of the stomach.

One antrum biopsy was used for on-site rapid urease test. Two antrum and one body biopsies were used for histology. *H. pylori* was presumptively identified by its morphology. The presence of tightly coiled spiral organisms (*Gastrospirillum hominis*) was excluded. Slides were read and reported as:

Grade 0	=	<i>H. pylori</i> non-visible (negative)
Grade 1	=	<15 <i>H. pylori</i> per slide
Grade 2	=	1-5 <i>H. pylori</i> per high power field (hpf)
Grade 3	=	6-20 <i>H. pylori</i> / hpf
Grade 4	=	21-100 <i>H. pylori</i> / hpf
Grade 5	=	>100 <i>H. pylori</i> / hpf

One biopsy from the antrum and one from body were used for metronidazole, clarithromycin, amoxicillin and tetracycline susceptibility. *In vitro* antimicrobial susceptibility tests of *H. pylori* isolates to clarithromycin and metronidazole was determined by the agar dilution method. The NCCLS has defined susceptibility to clarithromycin as shown in the following table.

**NCCLS Approved Breakpoints for Clarithromycin (Clinical Isolates)
Approved at Subcommittee Level on January 1999**

Antibiotic	MIC Range (µg/mL)
Susceptible	≤ 0.25 µg/mL
Intermediate	0.5 µg/mL
Resistant	≥ 1 µg/mL

A minimum inhibitory concentration (MIC) of ≥ 8 µg/mL for metronidazole was defined as resistant.

If the patient had a positive ¹³C-UBT at the End-of-Study or at the Confirmation Visit, the patient was to be re-endoscoped and two additional biopsies were taken, one from the antrum and one from the body of the stomach, for susceptibility testing against metronidazole and clarithromycin.

J. Efficacy Assessments

A patient was considered to be infected with *H. pylori* at baseline if the rapid urease test was positive and the results were later confirmed by ¹³C-UBT and either histology or culture.

For the determination of the presence of *H. pylori* in biopsies by histology and culture, both antrum and corpus were tested (two biopsies from the antrum and one from the corpus for histology, one biopsy from the antrum and one from the corpus for culture). In the case of discordant results for histology or culture between the antrum and the corpus biopsies, the presence of *H. pylori* was confirmed if at least one of the biopsies was positive for the organism. Uninterpretable results and insufficient tissue sampling were considered to be negative for *H. pylori*.

The main primary efficacy parameter is the absence (eradication) of *H. pylori* after treatment as assessed by ¹³C-UBT. Eradication was defined, according to guidelines, as two negative ¹³C-UBTs done at least 4 weeks (i.e., 28 days) and 8 weeks (i.e., 56 days) after the end of treatment.

K. Statistical Analyses and Evaluability Criteria

Statistical Analyses

The main data analysis performed by the applicant was a Modified Intent-to-treat (MITT) analysis, as requested in the 1997 Guidance, which included only patients who met the inclusion/exclusion criteria. A formal efficacy (Per Protocol) analysis was also done.

Clinical and Statistical Reviewers' Comments: The 1997 Guidance document recommends the MITT analysis be considered primary. However, the reviewers, as recommended by the Division, will also consider the consistency, or lack thereof, between the MITT and PP eradication analyses in this review. The reasons for exclusion from the MITT analysis are specified in the Results section.

The proportion of patients with eradication for each treatment was calculated. The 95% confidence interval for this proportion was constructed using normal approximation to binomial distribution.

Patients were subgrouped *a posteriori* by susceptibility or resistance to metronidazole and clarithromycin, and 95% confidence intervals were estimated for each subgroup of *H. pylori* isolates. For patients randomized to OBMT, the rate of eradication in patients with metronidazole resistant *H. pylori* was compared to that in patients with metronidazole susceptible *H. pylori* by the use of the likelihood ratio test. A similar analysis was done for resistance to clarithromycin in patients randomized to OAC treatment.

Patients with a history of duodenal ulcer in the preceding 2 years and those with a history greater than 2 years and less than or equal to 5 years were also subgrouped *a posteriori* and the 95% confidence intervals were estimated for each subgroup.

Secondary resistance was evaluated by using descriptive statistics to summarize the shift in susceptibility of isolates after treatment.

At FDA's request, an *a posteriori* analysis was also done comparing, for each treatment, the results in patients who have a $\geq 75\%$ drug compliance with those who have a $< 75\%$ drug compliance.

An *a posteriori* analysis was also done on eradication rate where patients with active ulcer disease were isolated from patients with a history of duodenal ulcer ≤ 2 years.

Clinical Reviewer's Comment: The Division did not request an analysis based on patients with an active versus history of ulcer; however, it was requested by Health Canada. Since applicant will use the results from this trial to support a Helizide application in both the US and Canada, this analysis is included in the study report, primarily for the benefit of Health Canada.

In order to compare the eradication rates obtained with OBMT with those obtained with OAC, a 95% confidence interval was constructed around the difference of 2 proportions using normal approximation to binomial distribution.

Since this trial was multi-center, the rate of eradication was generated for each center and compared descriptively. If needed, a unidimensional test for outliers was conducted.

Evaluability Criteria

Subjects who withdrew subsequent to the pre-study evaluations but before receiving any study medication were not included in the database.

Safety Population

All patients exposed to at least one dose of treatment were included in the safety population. Included in this population were those patients who were randomized to and began treatment, but later were declared *H. pylori* negative based on both histology and culture results.

Modified Intent-To-Treat (MITT) Population

Patients were excluded from the MITT population if they:

- Were not found to be *H. pylori* positive at screening by both ^{13}C -UBT and histology **OR** both ^{13}C -UBT and culture
- Did not have an adequately documented history of duodenal ulcer or an active duodenal ulcer
- Had any significant exclusion criteria*

* Patients could have been enrolled in the study before results of all pre-study tests were available. These patients were immediately withdrawn upon receipt of these results, if there was any evidence of major violation (e.g. in age, lab results, etc).

Clinical Reviewer's Comment: Exclusion of patients with protocol violations from the MITT population is not generally considered acceptable. In this study, only one patient in the OBMT group met this criterion and was excluded. The applicant's analysis will not be revised to include this one patient.

Per Protocol Population

The per protocol population excluded the following patients:

- Those excluded from the MITT population
- Those without results from two post-treatment tests
- Those with protocol deviations*
- Those who took forbidden medications (H₂-receptor antagonist, proton pump inhibitor, antibiotics, etc.)
- Those with ¹³C-UBTs done outside specified time windows [i.e., testing performed earlier than 28 days (first follow-up UBT) or 56 days (second follow-up UBT) after the end of treatment].

*Patients who took any part of the study medication, but failed to complete the course of treatment or the evaluation procedure was considered a dropout and was excluded from the per protocol population.

Clinical Reviewer's Comments: Dropouts during the treatment period where the reason for dropout is related to study medication or progression of disease should be included as failures.

It is recommended in the draft Eradication Guidance that patients who were non-compliant (defined as those who took < 75% of each medication and/or missed > 20% of consecutive doses of each medication) be excluded from the per-protocol population. At the Division's request, the applicant chose instead to do an a posteriori analysis comparing, for each treatment, the eradication results from patients who had a $\geq 75\%$ drug compliance with those who had < 75% drug compliance.

L. Results

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

1. Investigators

There were 51 investigator sites recruited for this study. Of those, 39 sites randomized at least 1 patient.

The number of patients enrolled per site and who received at least one dose of study medication (i.e., safety population) can be seen in Table 1 below. The mean number of patients enrolled was 8 per site (range 1-38). _____ has the highest enrollment at 12.7% (38/299) of the total population.

TABLE 1
Patient Enrollment by Site and Treatment Group
Safety Population (HPST99-CUS01)

Investigator Number	Investigator	Location	Treatment Group		Total
			OBMT	OAC	
02			4	2	6
03			3	2	5
04			1	1	2
31			1	1	2
05			3	2	5
07			1	1	2
08			5	5	10
09			1	1	2
10			4	7	11
11			6	5	11
12			6	9	15
13			5	3	8
34			2	2	4
35			2	2	4
36			--	1	1
37			7	12	19
38			--	1	1
15			2	3	5
29			2	2	4
39			16	9	25
23			1	--	1
43			3	4	7
19			4	4	8
24			1	--	1
25			2	1	3
45			2	2	4
46			2	1	3
47			1	--	1
48			15	23	38
44			11	16	27
49			9	6	15
52			11	15	26
54			4	2	6
55			3	2	5
26			1	1	2
28			3	2	5
27			1	2	3
21			2	--	2
		TOTALS	147	152	299

2. Patient Accountability

The number of patients who are included (considered evaluable) or excluded (considered non-evaluable) for the safety, MITT, and per protocol populations by treatment is shown in Table 2 according to the reasons for non-evaluability.

Clinical Reviewer's Data Validation Methods

Validation of the efficacy data was performed by reviewing the electronic and line listings of raw data for patients considered not evaluable by the applicant for either MITT or PP populations. Evaluability for both populations was made according to the draft Eradication Guidance.

In addition, 10% of the evaluable population (N=28) was randomly selected (blinded to treatment) and independently reviewed. The reviewer's assessment of evaluability corresponded to the applicant's for all patients in this sample.

TABLE 2
Disposition of Patients (HPST99-CUS01)

	TOTAL	OBMT	OAC
SUBJECTS SCREENED	783		
- Screening Failure	484		
= Received Drugs (Safety population)	299	147	152
- Excluded from MITT analysis	24	9	15
Found Hp negative after receiving drugs		0	7
No duodenal ulcer (active or history)		8	8
Should have not been treated: abnormal lab tests at entry		1	0
= MITT population	275	138	137
- Excluded from per protocol analysis	31	18	13
¹³ C UBTs done outside time windows		6	3
Lost to follow-up / voluntary withdrawal / death		6	4
Took a forbidden drug		6	5
Withdrawal due to adverse event		0	1
= Per protocol population	244	120	124

A listing of the patients excluded from the MITT and /or PP analyses and the reason for exclusion is included below.

Excluded from the MITT analysis

Found to be *H. pylori* negative after receiving drugs

Seven (7) patients in the OAC group were excluded from both the MITT and PP analyses because they received study drugs based on ¹³C-UBT or rapid urease test but were later found *H. pylori* negative by confirmatory testing.

Identification Numbers of Patients Excluded

OBMT	OAC
--	1010, 1109, 1308, 3914, 3923, 4403, 5239

*Clinical Reviewer's Comment: It is not clear why 7 *H. pylori* negative patients were found in the OAC group and none in the OBMT group. The investigators who enrolled these patients all enrolled multiple patients in both arms of the study, so technical error is unlikely. Three of the 7 patients had negative UBTs.*

No duodenal ulcer (active or history)

Sixteen (16) patients (8 in each group) were excluded from both the MITT and PP analyses because they were randomized despite absence of active duodenal ulcer or history of duodenal ulcer. This error was the result of misunderstanding of the protocol by some investigators.

Identification Numbers of Patients Excluded

OBMT	OAC
210, 501, 4302, 4316, 5405, 5408, 5410, 5504	202, 502, 504, 4304, 4307, 4310, 4315, 5404

Clinical Reviewer's Comment: Of the 8 OBMT patients without active duodenal ulcer or a history of ulcer disease, five were eradicated, two had a negative UBT at Day 28 and no second UBT performed. One patient was positive on Day 28 and no second UBT was performed. Of the 8 OAC patients, five were eradicated, two had a negative UBT at Day 28 and no second UBT performed, and one patient was positive by both follow-up UBTs (i.e., Day 28 and Day 56).

Should not have been treated: abnormal lab tests at entry

One patient randomized to OBMT (#1113) was excluded from both the MITT and PP analyses due to a protocol violation (i.e., significant neutropenia at baseline). He was enrolled prior to the availability of laboratory tests and immediately discontinued when the results became known.

Clinical Reviewer's Comment: Exclusion of patients with protocol violations from the MITT population is not generally considered acceptable. In this study, only one patient in the OBMT group met this criterion and was excluded. The applicant's analysis will not be revised to include this one patient.

Excluded from the PP Analysis

¹³C-UBTs done outside time windows

Nine (9) patients (6 in the OBMT and 3 in the OAC group) were excluded from the PP analysis because their ¹³C-UBT for the End-of-Study or Confirmation Visit was performed outside the allowed time windows [i.e., testing performed earlier than 28 days (end of study visit) or 56 days (confirmation visit) after the end of treatment]. For some patients a repeat visit, done within the window, reconfirmed the results obtained at a previous visit made outside the window. If both tests gave negative results, the visit was considered in compliance with guideline requirements.

Identification Numbers of Patients Excluded

OBMT	OAC
505, 3504, 3742, 4301, 4511, 5235	3908, 4502, 4601

Clinical Reviewer's Comment: Most of the above patients were excluded because their End-of-Study visit was < 28 days after the end of treatment (i.e., roughly 7 days early). The draft Eradication Guidance recommends that patients with a negative test result < 28 days after the end of treatment be excluded from the PP analysis. However, all of these patients had a second follow-up UBT performed 4 weeks later at the confirmation visit and all were negative. These patients could have been considered successes in the PP analysis, but there are only a few patients involved and the impact on the efficacy analysis is minimal. Therefore, the applicant's analysis was not be recalculated by the reviewer.

Lost to follow-up / voluntary withdrawal / death

In this category there were 10 patients (6 in the OBMT and 4 in the OAC group) who were excluded from the PP analysis.

Identification Numbers of Patients Excluded

OBMT	OAC
3102, 4878, 4893, 5209, 3921, 807 (death)	3918, 4810, 3715, 4883

Clinical Reviewer's Comments: OAC patient #4883 was excluded from the PP analysis and is listed in the lost to follow-ups/voluntary withdrawal category. However, this patient experienced adverse events during treatment (i.e., headaches, nausea, dizziness, and epigastric distress) and is also listed as a discontinuation. Since it appears that the true cause of her discontinuation is AEs related to study medication, she should have been included as a failure in the PP analysis. The applicant's PP analysis was recalculated to include this patient as a failure. Her bacterial isolate was resistant to clarithromycin (MIC =8 µg/mL) pre-treatment. See Tables 7A and 7B and Table 9.

One patient (#807) died 12 days after completing treatment with OBMT. The cause of death was listed as respiratory failure secondary to pneumonia and pulmonary fibrosis. The investigator judged the patient's death as unlikely to be related to study medication. The reviewer agrees with the investigators' assessment. It is unlikely that this patient's death was related to study drug. For more information on the case, refer to the Integrate Safety Summary (ISS).

Took a forbidden drug

Eleven (11) patients (6 in the OBMT and 5 in the OAC groups) were considered failures for the MITT analysis and excluded from the PP analysis because they took forbidden medications during the study. Explanations are given below in Table 3.

Clinical Reviewer's Comment: The applicant's definition of failures in the MITT analysis was more rigorous than suggested by the draft Eradication Guidance. In the Guidance, the definition of failures for the MITT analysis does not mention those patients who took forbidden medications. Of the six OBMT patients listed in Table 3 below, 4/4 with a follow-up UBT at Day 56 were negative. Of the five OAC patients, 3/3 with a follow-up UBT at Day 56 were negative.

TABLE 3
Patients Who Used Forbidden Medications During the Study (HPST99-CUS01)

PATIENT #	RECEIVED	FOR
OBMT		
2603	Amoxicillin	Influenza
2801	Pantoprazole	Prophylaxis of heartburn ⁽¹⁾
2804	Omeprazole	Prophylaxis of heartburn ⁽¹⁾
3501	Famotidine	Indigestion
4804	Amoxicillin Omeprazole, Famotidine	Bronchitis Duodenal ulcer
5409	Amoxicillin	Bronchitis
OAC		
701	Norfloxacin	Bladder infection
2802	Pantoprazole	Prophylaxis of heartburn ⁽¹⁾
2803	Pantoprazole	Prophylaxis of heartburn ⁽¹⁾
3503	Clarithromycin and Azithromycin	Sinusitis
3767	Famotidine	Indigestion

⁽¹⁾ The applicant noted that the Investigator at this site routinely gave PPIs after *H. pylori* eradication treatment. He did not notice that PPIs were not allowed in the protocol and treated four patients before the violation was discovered during a monitoring visit.

Withdrawal due to adverse event

One patient in the OAC group (#5242) was excluded from the PP analysis due to an adverse event.

Clinical Reviewer's Comments: Patient #5242 was withdrawn from the study medications after one day due to a possible allergic reaction. Since the adverse event was probably due to the study medication, this patient should have remained in the PP analysis as a failure. The applicant's analyses was recalculated to include this patient. His bacterial isolate was susceptible to clarithromycin pre-treatment. See Tables 7A and 7B and Table 9.

Other Minor Deviations, not resulting in patient withdrawal

As allowed by the protocol, some patients took occasional doses of PPIs or H₂-receptor antagonists in the days preceding screening. Since these drugs are at risk of causing false negative results (resulting in excluding a valid patient) and not false positive results (resulting in inclusion of a non-valid patient) this was considered a minor deviation by the applicant. If the ¹³C-UBT done at screening was positive (confirmed by histology or culture) the patient was included in the trial.

Clinical Reviewer's Comment: The practice of including patients in the study who took occasional doses of acid-suppressing medications in the 2 weeks prior to screening with a positive screening ¹³C-UBT is considered acceptable.

Despite the exclusion criteria about the use of NSAID, some investigators did not consider COX-2 specific inhibitors as NSAIDs. This was found *a posteriori* by the applicant during monitoring visits. Since NSAIDs cause a safety issue and not an efficacy issue, the applicant did not withdraw these patients.

Clinical Reviewer's Comment: The practice of including patients in the analysis who took concomitant COX-2 specific inhibitors during the study is considered acceptable.

3. Demographic Characteristics

Patient baseline demographics are presented in Table 4 and ulcer disease history is presented in Table 5 below. Percentages are based on the number of patients in the Safety Population for each treatment group. The results are similar between the two treatment groups.

**Appears This Way
On Original**

TABLE 4
Demographic Characteristics
Safety Population (HPST99-CUS01)

Parameter	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients	N	147	152
Age (years)	n	147	152
	Mean	46.52	47.89
	Std	13.60	14.52
	Median	45.5	47.5
	Min., Max.	19.2, 75.6	18.1, 74.1
Sex			
Male	n (%)	90 (61.2%)	87 (57.2%)
Female	n (%)	57 (38.8%)	65 (42.8%)
Weight (kg)	n	147	152
	Mean	76.06	77.41
	Std	14.53	16.26
	Median	75.0	77.3
	Min., Max.	43.0, 115.9	46.0, 128.2
Height (cm)	n	147	151
	Mean	168.01	167.35
	Std	9.72	9.75
	Median	167.6	167.6
	Min., Max.	144.8, 190.5	142.2, 188.0
Race			
Unknown	n (%)	1 (0.7%)	0
Caucasian	n (%)	84 (57.1%)	92 (60.5%)
Black	n (%)	21 (14.3%)	12 (7.9%)
Asian	n (%)	11 (7.5%)	4 (2.6%)
Other	n (%)	30 (20.4%)	44 (28.9%)

Table 5 shows the number of patients in the safety population with a history of duodenal ulcer. Patients may also have had a history of gastric ulcer and/or non-ulcer dyspepsia.

TABLE 5
Ulcer Disease History
Safety Population (HPST99-CUS01)

Parameter	Statistic	Treatment Group	
		OBMT	OAC
Number of Patients in the Safety Population	N	147	152
History of Gastric Ulcer			
Yes	n (%)	20 (13.6%)	20 (13.2%)
No	n (%)	126 (85.7%)	131 (86.2%)
Unknown	n (%)	1 (0.7%)	1 (0.7%)
History of Duodenal Ulcer			
Yes	n (%)	92 (62.6%)	84 (55.3%)
No	n (%)	55 (37.4%)	68 (44.7%)
History of Non-Ulcer Dyspepsia			
Yes	n (%)	16 (10.9%)	30 (19.7%)
No	n (%)	130 (88.4%)	122 (80.3%)
Unknown	n (%)	1 (0.7%)	0

4. Compliance Results

Compliance in the safety population is shown below in Table 6. Approximately 90% of patients in both the OBMT and OAC groups were compliance with study medication, defined as $\geq 75\%$ of capsules taken and based on the number of returned capsules.

TABLE 6
Compliance with Study Medications
Safety Population (HPST99-CUS01)

Treatment	Compliance $\geq 75\%$	Compliance $< 75\%$
OBMT	132/147 (89.8%)	15/147 (10.2%)
OAC	142/152 (93.4%)	10/152 (6.6%)

5. Eradication

Overall Eradication

Eradication in the MITT and PP analyses by treatment group can be seen in Tables 7A and 7B below.

Clinical Reviewer's Comment: Tables 7A and 7B were created by the reviewer and not the applicant. Table 7A represents the applicant's analysis and Table 7B represents the FDA

reviewers' analysis (inclusion of two extra patients as failures in the PP population for the OAC group).

TABLE 7A
***H. pylori* Eradication at the Day 56 Visit**
Per Protocol and Modified Intent-to-Treat Analyses
(HPST99-CUS01)
Applicant's Analysis

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]
Per Protocol	111/120 (92.5) [87.8; 97.2]	108/124 (87.1) [81.2; 93.0]	5.4 [-2.1; 13.0]
Modified Intent-to- Treat	121/138 (87.7) [82.2; 93.2]	114/137 (83.2) [77.0; 89.5]	4.5 [-3.9; 12.8]

TABLE 7B
***H. pylori* Eradication at Day 56 Visit**
Per Protocol and Modified Intent-to-Treat Analyses
(HPST99-CUS01)
FDA Clinical and Statistical Reviewers' Analysis

<i>H. pylori</i> Eradicated Follow- up Visit	OBMT	OAC	Difference (OBMT – OAC)
	n/N (%) [95% CI]	n/N (%) [95% CI]	% [95% CI]*
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/126 (85.7) [79.6, 91.8]	6.1 [-0.9, 13.7]
Modified Intent-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

* 95% Confidence Interval for the difference in proportions (OBMT- OAC) is calculated using normal approximation to binomial distribution

*Clinical Reviewer's Comment: There are two patients in the OBMT group and one in the OAC group with discrepant results between the first and second UBT (i.e., the first was negative and the second was positive). Both OBMT patients have follow-up endoscopies. One patient (#4859) had a biopsy obtained for culture during the endoscopy, which later grew *H. pylori*. It is not clear from the other patient's data (#2301) whether a biopsy was obtained and the culture was negative or whether no specimen was obtained. The OAC patient (#3764) refused the endoscopy and withdrew consent.*

OBMT achieves numerically higher eradication rates than OAC. The lower bound of the 95% confidence interval of the difference in eradication rates (OBMT minus OAC) is –3.9% and –0.9% for the MITT and PP analyses (PP analysis conducted by the FDA reviewers), respectively.

*Clinical Reviewer's Comment: The applicant has followed the guidance provided by the Division during the development of Helizide for determining efficacy against *H. pylori*. The*

following recommendations were made to the applicant regarding establishment of an efficacy threshold.

- Active controlled studies are strongly recommended and should be powered for statistical equivalence or superiority. The investigational regimen will be considered similar to the approved comparator if the lower bound of the 95% two-sided confidence interval for the difference in eradication rates (investigational regimen minus approved active therapy) lies above -15%.
- The sponsor should discuss the choice of comparator regimens well in advance of beginning the study since it is recognized that some FDA approved regimens may be less ideal for comparative trials.

The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT versus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Although the delta was not specified in the study protocol, the confidence intervals are above the recommended non-inferiority margin of -15% and therefore provide evidence of the efficacy of Helizide (OBMT) therapy.

Eradication by Demographic Subgroup

The applicant did not subcategorize eradication rates at the Day 56 visit based on age, gender, or race.

Statistical Reviewer's Comment: Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories were performed to determine whether any of these covariates had a significant effect on H. pylori eradication rates. Although the sample size in each strata were small, the results do not indicate that any of these covariates had a statistically significant effect on eradication status.

Eradication by Antimicrobial Susceptibility

MITT Population

In the OBMT group, metronidazole susceptibility was successfully assessed pre-treatment in 125 isolates; 51 (40.8%) isolates were resistant to metronidazole and 74 (59.2%) were susceptible.

In the OAC group, clarithromycin susceptibility was successfully assessed pre-treatment in 114 isolates; 14 (12.2%) isolates were resistant to clarithromycin, none were of intermediate sensitivity, and 101 (87.8%) were susceptible.

Eradication rates based on pre-treatment susceptibility to metronidazole and clarithromycin for the MITT population are shown in Table 8 below.

Clinical Reviewer's Comments: Table 8 was created by the reviewer.

The applicant defines metronidazole resistance as a MIC \geq 8 μ g/mL. Yet, they refer to

Instead, the reviewer has presented the metronidazole data in Table 8 using MIC values of $\leq 8 \mu\text{g/mL}$ and $\geq 16 \mu\text{g/mL}$.

TABLE 8
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
MITT Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	MIC $\leq 8 \mu\text{g/mL}$	MIC $\geq 16 \mu\text{g/mL}$	Difference (≤ 8 minus ≥ 16) [95% CI]*	Susceptible	Resistant	Difference (Sus. – Res.) [95% CI]*
OBMT	68/74 (91.9)	41/51 (80.4)	11.5 [-0.1, 25.7]	ND	ND	ND
OAC	ND	ND	ND	93/101 (92.1)	3/14 (21.4)	70.7 [43.7, 85.4]

ND = not done

* 95% Confidence Interval for the difference in proportions (Susceptible - Resistant) is calculated using an exact method.

Clinical and Statistical Reviewers' Comment: The difference in eradication rates in the OBMT group between isolates with a metronidazole MIC $\leq 8 \mu\text{g/mL}$ and $\geq 16 \mu\text{g/mL}$ in the MITT population was calculated by the reviewers and found to be 11.5%. The 95% confidence interval for the difference in eradication rates includes zero and suggests that for OBMT treated patients, the rate of eradication in patients is similar whether the isolate has a metronidazole MIC of $\leq 8 \mu\text{g/mL}$ or $\geq 16 \mu\text{g/mL}$.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates was calculated by the reviewers and found to be 70.7%. The 95% confidence interval for the difference in eradication rates does not include zero and affords the conclusion that for OAC treated patients, the rate of eradication in the resistant group is at least 43.7% lower than that of the susceptible group. The difference in eradication rates between susceptible and resistant isolates may be more clinically meaningful for clarithromycin than the difference between isolates with a MIC of $\leq 8 \mu\text{g/mL}$ and $\geq 16 \mu\text{g/mL}$ for metronidazole.

Per Protocol Population

In the OBMT group, metronidazole susceptibility was successfully assessed pre-treatment in 108 isolates; 44 (40.7%) isolates were resistant to metronidazole and 64 (59.3%) were susceptible.

In the OAC group, clarithromycin susceptibility was successfully assessed pre-treatment in 106 isolates; 13 (12.2%) isolates were resistant to clarithromycin, none were intermediate, and 93 (87.8%) were susceptible.

Eradication rates based on pre-treatment susceptibility to metronidazole and clarithromycin for the MITT population are shown in Table 9 below.

Clinical Reviewer's Comment: Table 9 was created by the reviewer. Comment regarding Table 8 applies to Table 9, as well.

TABLE 9
Eradication Rates (%) by Pre-Treatment Antimicrobial Susceptibility
PP Population (HPST99-CUS01)

	Metronidazole Susceptibility			Clarithromycin Susceptibility		
	MIC ≤ 8µg/mL	MIC ≥ 16µg/mL	Difference (≤ 8 minus ≥ 16) [95% CI]*	Susceptible	Resistant	Difference (Sus. – Res.) [95% CI]*
OBMT	61/64 (95.3)	38/44 (86.4)	8.9 [-2.0, 23.5]	ND	ND	ND
OAC	ND	ND	ND	88/93 (94.6)	3/13 (23.1)	71.6 [43.6, 87.1]

ND = not done

* 95% Confidence Interval for the difference in proportions (Susceptible - Resistant) is calculated using an exact method.

Clinical and Statistical Reviewers' Comment: The difference in eradication rates in the OBMT group between isolates with a metronidazole MIC < 8 µg/mL and ≥ 8 µg/mL in the MITT population was calculated by the reviewers and found to be 8.9%. The 95% confidence interval for the difference in eradication rates includes zero and affords the conclusion that for OBMT treated patients, the rate of eradication in patients is similar whether the isolate has a metronidazole MIC of ≤ 8 µg/mL or ≥ 16 µg/mL.

The difference in eradication rates in the OAC group between clarithromycin susceptible and resistant isolates calculated by the reviewer and was found to be 71.6%. The 95% confidence interval for the difference in eradication rates does not include zero and affords the conclusion that for OAC treated patients, the rate of eradication in the resistant group is at least 43.6% lower than that of the susceptible group. The difference in eradication rates between susceptible and resistant isolates may be more clinically meaningful for clarithromycin than the difference between isolates with a MIC of ≤ 8 µg/mL and ≥ 16 µg/mL for metronidazole.

Eradication by Duration of Disease

MITT Population

In the OBMT group, 15 (10.9%) patients have an active duodenal ulcer, 114 (82.6%) patients have a history of duodenal ulcer ≤ 2 years ago and 9 patients (6.5%) have a history of duodenal ulcer > 2 years ago.

In the OAC group, 13 (9.5%) patients have an active duodenal ulcer, 116 (84.7%) patients have a history of duodenal ulcer ≤ 2 years ago, and 8 (5.6%) patients have a history of duodenal ulcer > 2 years ago.

Eradication rates for patients with active duodenal ulcers compared to those with a history of ulcer disease are shown in Tables 10 and 11 by treatment group for the MITT and PP analyses, respectively.

Clinical Reviewer's Comment: Tables 10 and 11 were adapted by the reviewer from the applicant's original tables. The statistical reviewer recalculated the applicant's confidence intervals using an exact method.

TABLE 10
Eradication Rates (n/N) [95% CI] by Disease History
MITT Population (HPST99-CUS01)

Treatment	Active Duodenal Ulcer	History of Duodenal Ulcer	
		≤ 2 years ago	> 2 and ≤ 5 years ago
OBMT	100% (15/15) [78.2, 100.0]	85.1% (97 / 114) [77.2, 91.1]	100% (12/12) [73.5, 100.0]
OAC	92.3% (12/13) [64.0, 99.8]	82.8% (96 / 116) [74.6, 89.1]	75% (6/8) [34.9, 96.8]

* 95% Confidence Interval is calculated using an exact method.

Per Protocol Population

In the OBMT group, 14 (11.7%) patients have an active duodenal ulcer, 97 (80.8%) patients have a history of duodenal ulcer ≤ 2 years ago and 9 patients (7.5%) have a history of duodenal ulcer > 2 years ago.

In the OAC group, 12 (9.7%) patients have an active duodenal ulcer, 104 (83.9%) patients have a history of duodenal ulcer ≤ 2 years ago, and 8 (6.5%) patients have a history of duodenal ulcer > 2 years ago.

Eradication rates for patients with active duodenal ulcers compared to those with a history of ulcer disease for the PP population are shown in Table 11 by treatment group. Given the small number of patients in the groups with an active ulcer and with a history of duodenal ulcer > 2 years ago, statistical comparisons were not attempted by the applicant.

TABLE 11
Eradication Rates (n/N) [95% CI]* by Disease History
PP Population (HPST99-CUS01)

Treatment	Active Duodenal ulcer	History of Duodenal Ulcer	
		≤ 2 years ago	> 2 and ≤ 5 years ago
OBMT	100% (14/14) [76.8, 100.0]	90.7% (88/97) [83.1, 95.7]	100% (9/9) [66.4, 100.0]
OAC	91.7% (11/12) [61.5, 99.8]	87.5% (91/104) [90.0, 93.2]	75% (6/8) [34.9, 96.8]

* 95% Confidence Interval is calculated using an exact method.

Eradication by Compliance

MITT Population

Twenty-one (21) patients (14.9%) were compliant with < 75% of study capsules (10.4% patients in the OBMT group and 6.2% patients in the OAC group). Table 12 shows the effect of compliance on eradication rates. For both groups compliance < 75% results in a numerically lower eradication rate. However, *a posteriori* comparisons by Fisher's test did not show a statistically significant difference between treatment groups in eradication when stratified by compliance with study medications.

TABLE 12
Eradication Rates by Compliance to Medications
MITT population (HPST99-CUS01)

Sub-population	OBMT	OAC
Compliance \geq 75%	113/125 (90.4%)	111/129 (86.0%)
Compliance < 75%	8/13 (61.5%)	3/8 (37.5%)

Per Protocol Population

Thirteen (13) patients (5.6%) were compliant with < 75% of study capsules (7.5% patients in the OBMT group and 3.3% patients in the OAC group). Table 13 shows the effect of compliance on eradication rates. For both groups compliance < 75% results in a numerically lower eradication rate. However, a *posteriori* comparisons by Fisher's test did not show a statistically significant difference between treatment groups in eradication when stratified by compliance with study medications.

TABLE 13
Eradication Rates by Compliance to Medications
PP population (HPST99-CUS01)

Sub-population	OBMT	OAC
Compliance \geq 75%	104/111 (93.7%)	106/120 (88.3%)
Compliance < 75%	7/9 (77.8%)	2/4 (50.0%)

6. Evaluability Status

Baseline *H. pylori* infection status based on results of the three pre-treatment endoscopic tests in the safety population is presented in Table 14. The results of the rapid urease test were using only for screening purposes and was not a confirmatory test. In addition to the endoscopic tests, all patients were positive by ¹³C-UBT. Most patients had three tests available and were positive by all three or at least by histology and rapid urease test.

**Appears This Way
On Original**

TABLE 14
Classification of *H. pylori* Infection
Based on Endoscopic Tests for *H. pylori* at Baseline
Safety Population
(HPST99-CUS01)

Pre-therapy (Baseline) Diagnosis				
Culture	Histology	Rapid Urease Test	OBMT (N=147)	OAC (N=152)
Three tests available				
+	+	+	130	117
+	+	-	0	2
+	-	+	0	1
+	-	-	1	0
-	+	+	15	22
-	-	+	0	1
-	+	-	0	1
-	-	-	0	2
Two tests available				
+	+	N/A	0	0
+	-	N/A	0	0
-	+	N/A	0	0
-	-	N/A	0	2*
+	N/A	+	0	0
+	N/A	-	0	0
-	NA	+	0	0
-	NA	-	0	0
N/A	+	+	1	2
N/A	+	-	0	0
N/A	-	+	0	0
N/A	-	-	0	0
Zero or one test available				
+	N/A	N/A	0	0
-	N/A	N/A	0	0
N/A	N/A	+	0	1
N/A	N/A	-	0	0
N/A	+	N/A	0	0
N/A	-	N/A	0	1**
N/A	N/A	N/A	0	0

* rapid urease test was performed, in addition to culture and histology, but the results were inconclusive for both patients

** rapid urease test was performed, in addition to histology (culture not available), but the results were inconclusive

Clinical Reviewer's Comments: Since endoscopy was only performed in a small subset of patients with a positive UBT post-therapy, a similar table was not created for the post-therapy data.

7. Susceptibility

Among assessable *H. pylori* isolates, pre-treatment resistance is 40.7% for metronidazole, 11.5% for clarithromycin, 2.8 % for tetracycline, and 0.4% for amoxicillin.

Changes in susceptibility to clarithromycin and metronidazole were assessed post-treatment in patients who failed eradication. Unfortunately, many patients refused to have a second endoscopy after treatment. Available results for metronidazole and clarithromycin are presented for the MITT population in Table 15 below.

Statistical Reviewer's Comment: Table 15 should be interpreted with caution as the small number of patients for which data are available most likely are not representative of the entire original MITT population.

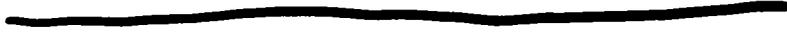
Clinical Reviewer's Comment: Table 15 was adapted from two of the applicant's tables by the reviewer.

TABLE 15
Baseline *H. pylori* Susceptibility Results vs. Eradication Status After Treatment
MITT Population (HPST99-CUS01)

Susceptibility to Metronidazole at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy			Susceptibility to Clarithromycin at baseline	<i>H. pylori</i> not eradicated	Susceptibility at second endoscopy		
		R	S	M			R	S	M
Resistant	10	5		5	Resistant	11	8		3
Susceptible	6	1		5	Susceptible	8	1	1	6
Missing	1			1	Missing	4	1		3
Total	17				Total	23			

R = resistant; S = susceptible; M = Missing
 Metronidazole: R ≥ 8 µg/mL; S ≤ 4 µg/mL
 Clarithromycin: R ≥ 1 µg/mL; S ≤ 0.25 µg/mL

Clinical Reviewer's Comment: The applicant defines metronidazole resistance as a MIC ≥ 8 µg/mL.



Instead, the same data can be represented using MIC values as shown in Table 16 below, which was created by the FDA reviewing microbiologist and is consistent with other labels for drugs approved for this indication.

TABLE 16
Metronidazole Susceptibility Test Results and
Clinical/Bacteriological Outcomes^a for HELIZIDE Therapy
(Three HELIZIDE® capsules four times a day
plus omeprazole 20 mg twice daily for 10 days)

Metronidazole Pretreatment Results	<i>H. pylori</i> negative (Eradicated)	<i>H. pylori</i> positive (Not Eradicated) Post-treatment susceptibility results		
		MIC ≤ 8	MIC ≥ 16	No MIC
MIC ≤ 8 µg/mL 74	67	0	2	5
MIC ≥ 16 µg/mL 51	42	0	4	5

^a Includes only patients with pretreatment metronidazole susceptibility test results

8. Safety Analyses

The Safety results from Study HPST99-CUS01 can be found in the Integrated Summary of Safety (ISS).

M. Clinical and Statistical Reviewers' Conclusions of Study HPST99-CUS01

This is a well conducted, randomized, active-controlled clinical trial that demonstrated the non-inferiority of OBMT versus OAC when given for 10 days. The lower bound of the 95% confidence intervals for the difference in eradication rates for the OBMT minus OAC groups are -3.9% and -0.9% for the MITT and PP analyses, respectively. Therefore, the confidence intervals are above a non-inferiority margin of - 15% and provide evidence of the efficacy of Helizide plus omeprazole therapy (OBMT) in the treatment of *H. pylori* infection.

Other findings include:

- Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories do not indicate that any of these covariates had a statistically significant effect on eradication status, although the sample size in each strata was small.
- The rate of eradication in patients treated with OBMT having a pre-treatment bacterial isolate with a metronidazole MIC ≤ 8 µg/mL is similar to patients having an isolate with a metronidazole MIC ≥ 16 µg/mL in both the MITT and PP analyses. Conversely, in the OAC group the rate of eradication in patients whose bacterial isolates pre-treatment are resistant to clarithromycin (defined as an MIC ≥ 1 µg/mL) is statistically inferior to patients having a susceptible clarithromycin pre-treatment isolate.
- No conclusions can be drawn regarding the rates of emerging resistance to either OBMT or OAC due to the few number of patients with culture results available post-treatment.

APPENDIX 5 – PROPOSED LABEL (9/5/03)

blank page

21 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical-5

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joette Meyer
10/2/03 11:50:30 AM
MEDICAL OFFICER

Rigoberto Roca
10/2/03 11:52:47 AM
MEDICAL OFFICER

Karen Higgins
10/2/03 03:06:42 PM
BIOMETRICS
signing for Ruthanna Davi

Karen Higgins
10/2/03 03:07:22 PM
BIOMETRICS

Edward Cox
10/2/03 03:33:19 PM
MEDICAL OFFICER

Deputy Office Director's and Division Director's Memo

**NDA 50-786
Helizide® Capsules
(biskalcitrate potassium/metronidazole/tetracycline hydrochloride)**

Date: October 2, 2003

From: Edward M. Cox, MD, MPH
Deputy Director, Office of Drug Evaluation IV, HFD-104

Renata Albrecht, MD
Director, DSPIDP, HFD-590

To: NDA 50-786

Re: Helizide® (biskalcitrate potassium/metronidazole/tetracycline hydrochloride)
CanReg, Inc., U.S. agent representing Axcan Scandipharma, Inc.

Original submission date: October 2, 2001 (CDER stamp date)
First Action Letter Date: August 12, 2002
First Action: Not Approvable

Resubmission Date: April 2, 2003 (CDER stamp date)
Action Date: October 2, 2003

Deputy Office Director's and Division Director's Recommended Regulatory Action:

Not Approvable for NDA 50-786 Helizide (biskalcitrate potassium/metronidazole/tetracycline hydrochloride).

Deficiencies

1. During a recent inspection for NDA 50-786 of the _____ our field investigator conveyed deficiencies to the facility's representatives. Some of these deficiencies had been noted in a previous inspection. Satisfactory resolution to these deficiencies is required before this application may be approved.

At the time of the re-submission for NDA 50-786, an update on the adverse events reported for Helizide based upon post-marketing experience from

countries where Helizide is marketed, specifically including an update and summary on any hepatic adverse events should be provided.

In addition, it will be necessary to revise the package insert prior to approval.

Background

There are 6 FDA approved three-drug regimens for the treatment (eradication) of *H. pylori* in patients with an active, or a history of, duodenal ulcer. Among the FDA approved regimens is Helidac® (NDA 50-719, approved in 1996). Helidac is comprised of bismuth subsalicylate 525 mg po QID + metronidazole 250 mg po QID + tetracycline 500 mg po QID to be taken in combination with an H₂-receptor antagonist (at treatment doses for an active duodenal ulcer) for 14 days.

Practice guidelines from the American College of Gastroenterology also include among the list of recommended therapies combination regimens that include bismuth, metronidazole, tetracycline, and a proton pump inhibitor.¹

The components of Helizide are biscalcitate potassium, metronidazole, and tetracycline hydrochloride. Helizide provides a total daily dose of biscalcitate potassium 1680 mg (480 mg as Bi₂O₃ equivalent), metronidazole 1.5 grams, and tetracycline 1.5 grams. Helizide is to be used in combination with omeprazole. The duration of Helizide treatment is 10 days.

The total daily exposures for the components of Helizide are within the range of previously approved dosages and durations for the component drugs metronidazole and tetracycline. Metronidazole is approved for use at total daily doses up to 2.250 grams for durations of up to 10 days with a notation that certain types of infections may require longer durations of therapy. Tetracycline is approved for total daily dosages of 2 grams for durations up to 3 weeks for certain types of infections. Biscalcitate potassium is similar to colloidal bismuth subcitrate which is the active ingredient in De-Noltab®, an approved drug product in Europe which provides daily dose of Bi₂O₃ equivalent to approximately 480 mg daily for durations of up to 8 weeks. The total daily dose of Bi₂O₃ delivered in the Helidac regimen is 816 mg. In the US other bismuth containing preparations are available including several formulations of Pepto-Bismol®. Omeprazole (not part of Helizide) is used in conjunction with Helizide at its approved dosage for 10 days.

¹ Howden CW, Hunt RH. Guidelines for the management of Helicobacter pylori infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol. 1998 Dec;93(12):2330-8.

NDA 50-786

NDA 50-786 was originally submitted on October 2, 2001. The application was submitted as a 505(b)(2) application in that it relied upon the agency's previous finding of safety and efficacy for the previously approved product Helidac® and also relied upon published literature. The application included the results of clinical pharmacology studies, a pivotal phase III comparative clinical study, and a supportive non-comparative clinical study. The result of the initial review cycle was a not approvable action on August 12, 2002. The deficiencies in the action letter of August 12, 2002 were as follows:

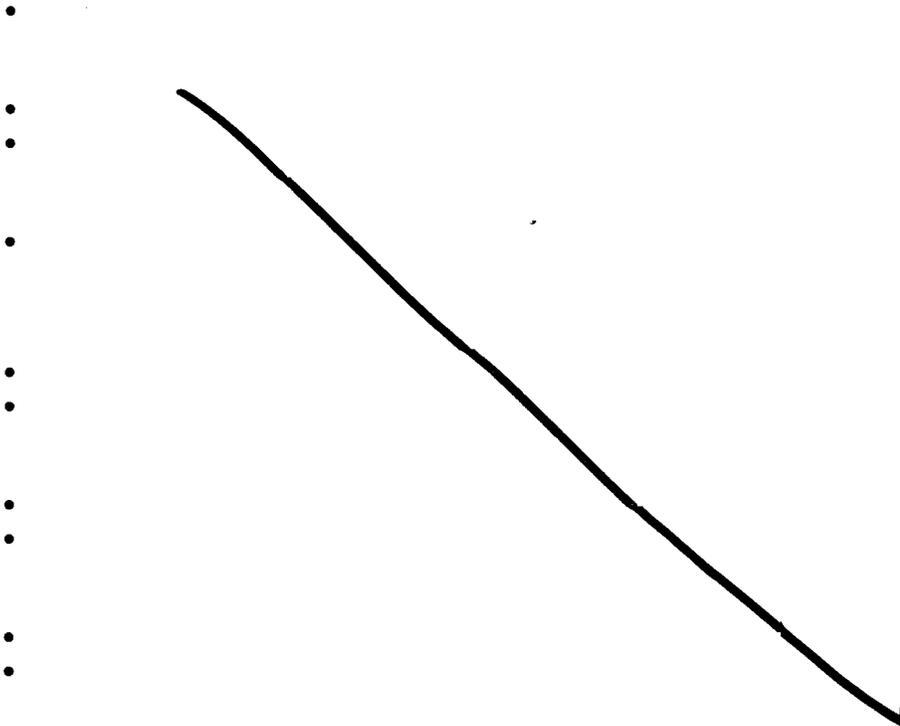
1. In a letter dated April 19, 2002, deficiencies to DMF [redacted] were conveyed to the DMF holder, [redacted], through their U.S. agent. Some of these deficiencies are approvability issues. At this time, no response has been received.
2. Deficiencies in the drug substance section of the NDA were conveyed to the applicant on June 18, 2002. Some of these deficiencies are approvability issues.
3. The data submitted in support of [the Applicant's] proposed dissolution method are inadequate for evaluation. [The Applicant] must submit dissolution profiles obtained with [redacted]

During a recent inspection for [the Applicant's] NDA of the [redacted] [redacted] a number of deficiencies were noted and conveyed to [the Applicant or the Applicant's] supplier by the investigator. Under 21 CFR 314.125(b)(13), these deficiencies must be satisfactorily resolved before approval.

The August 12, 2002 action letter also notes that it will also be necessary to revise the package insert and that we anticipate that labeling discussions will take place prior to approval.

NDA 50-786 was resubmitted on April 2, 2003 (CDER stamp date). The Chemistry review and inspections of the manufacturing facilities note deficiencies identified during the inspection of the [redacted] [redacted] the producer of biscalcitrates drug substance. On the basis of the identified deficiencies, the Office of Compliance has issued a withhold recommendation. Some of the major deficiencies from the September 2003 inspection as noted in Dr. Gene Holbert's Chemistry Review are reproduced below:

- [redacted] used to produce biscalcitrates were never calibrated. When found out of calibration, no investigation was undertaken to determine the possible impact on the drug substance.
- [redacted]



Of note is that some of these items had been noted in the previous inspection.

With regards to pharmacology and toxicology studies, the applicant has utilized a 505(b)(2) approach and hence relied upon published information on the pharmacology and toxicology for the component drugs. A study report for a 6-month rat and a 6-month dog study evaluating bismuth subcitrate at human equivalent doses up to 4.8 mg/kg/day and 10 mg/kg/day (rat and dog studies, respectively) found no adverse effects including no adverse hepatic effects. The studies included histopathologic examination at necropsy. The human dosing regimen of biscalcitrates is approximately 7 mg/kg/day.

A bioavailability study of a single dose of Helizide compared to a single dose of 3 separate capsule formulations of the components of Helizide [metronidazole (375 mg), tetracycline (375 mg) and biscalcitrates potassium (140 mg)] was performed under fasting and fed conditions. The C_{max} and AUC achieved for metronidazole were bioequivalent for Helizide compared to the separate capsule formulation. For tetracycline and bismuth, the C_{max} and AUC were less for Helizide than for the separate capsules of tetracycline and bismuth. The T_{max} and $T_{1/2}$ were similar for Helizide and its individual components in the separate capsule formulations. Food reduced the bioavailability of Helizide with the following reductions in AUC for each of the components in Helizide: metronidazole, 6%; tetracycline, 34%; and bismuth, 60%. Helizide is recommended to be taken with omeprazole at meals and at bedtime. This

recommendation is consistent with the manner in which the drug was administered in the pivotal clinical trial.

The application includes a pivotal randomized, open-label, active controlled trial comparing Helizide plus omeprazole to the approved regimen of omeprazole, amoxicillin, and clarithromycin for the eradication of *H. pylori* in patients with an active, or history of, a duodenal ulcer. The study enrolled 147 patients in the Helizide arm and 152 patients in the comparator arm. The Helizide regimen was found to be non-inferior to the comparator regimen (Table 1).

Table 1.
***H. pylori* Eradication at Day 56 Visit**
Per Protocol and Modified Intent-to-Treat Analyses
Pivotal Comparative Study

<i>H. pylori</i> Eradicated Follow-up Visit	Helizide Omeprazole (OBMT) n/N (%) [95% CI]	Omeprazole Amoxicillin Clarithromycin (OAC) n/N (%) [95% CI]	Difference (OMBT – OAC) % [95% CI]*
Per Protocol	111/120 (92.5) [87.8, 97.2]	108/126 (85.7) [79.6, 91.8]	6.1 [-0.9, 13.7]
Modified Intent-to-Treat	121/138 (87.7) [82.2, 93.2]	114/137 (83.2) [77.0, 89.5]	4.5 [-3.9, 12.8]

* 95% Confidence Interval for the difference in proportions (OBMT- OAC) is calculated using normal approximation to binomial distribution

An additional non-comparative study that enrolled 177 patients was performed that provided corroborating evidence for efficacy of Helizide in the eradication of *H. pylori*. The eradication rates for the non-comparative study were 97.3% in the Per Protocol Population and 92.9% in the Modified-Intent-to-Treat (MITT) population (Table 2).

Table 2.
Overall *H. pylori* Eradication at the Day 56 Visit
Per Protocol and Modified Intent-to-Treat Analyses
Non-Comparative Study

	Per-Protocol n/N (%) [95% CI]*	MITT n/N (%) [95% CI]*
Helizide	142/146 (97.3) [93.1, 99.3]	158/170 (92.9) [88.0, 96.3]
Omeprazole		

* 95% Confidence Interval is calculated using an exact method.

The clinical studies performed by the sponsor included a total of 383 patients exposed to Helizide in either phase I or phase III studies (324 of these 383 patients received Helizide in one of the two phase III studies). In the pivotal comparative study, in general, adverse event rates were similar between treatment groups. Patients receiving Helizide plus omeprazole more frequently reported darkening of the stool (likely related to bismuth) (15.6% vs. 4.6%). Taste perversion was reported more commonly in the comparator group (11.8% vs. 4.8%). In the Helizide group 3/147 (2%) patients experienced increase in SGPT and 2/147 (1%) experienced increases in SGOT as adverse events. The elevation in SGPT were in the range of 2 to 3 times the upper limit of normal for two of the patients and 2 to 4 times the upper limit of normal for one of the patients. Following completion of therapy, the patients' transaminase levels were trending toward normal on follow-up laboratories. Adverse events involving increases in transaminases were not reported in the comparator arm. In the non-comparative study 6/177 patients (3%) experienced SGPT increases. Four of these six patients had an elevated SGPT at baseline; two of the patients had normal SGPT values at baseline. The elevations in the two patients normal at baseline were in the range of 3 to 5 times the upper limit of normal. For the six patients from the non-comparative study, data is also available on bilirubin levels; none of the 6 patients with elevated transaminases experienced concomitant elevations of bilirubin. The label for omeprazole states that adverse events, including elevations in SGPT and SGOT have been noted. Tetracycline is also known to have the capacity to cause hepatic adverse events.

NDA 50-786 is a 505(b)(2) application. In addition to the clinical studies performed by the sponsor, the application also relies upon the agency's finding of safety and efficacy for Helidac, which is a regimen of bismuth subsalicylate, metronidazole, and tetracycline to be used in combination with an H₂ antagonist, for the eradication of *H. pylori* in patients with an active, or history of, duodenal ulcer. In addition, the applicant has also provided supportive evidence from the literature on the clinical efficacy of bismuth, metronidazole, tetracycline and omeprazole for the treatment of *H. pylori*.

Summary

In summary, the application is not approvable due to the deficiencies noted during the inspection of the _____ facility for this NDA. The clinical efficacy data support efficacy of Helizide when used in combination with omeprazole in the eradication of *H. pylori* in patients with an active, or a history of, duodenal ulcer. At the time of re-submission, the applicant will also be requested to provide an update on the adverse events reported for Helizide based upon post-marketing experience from countries where Helizide is marketed, specifically including an update on any hepatic adverse events.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Edward Cox
10/2/03 03:48:21 PM
MEDICAL OFFICER

Renata Albrecht
10/2/03 04:58:44 PM
MEDICAL OFFICER