CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-636

Medical Review(s)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	21-636
Sponsor:	Santarus, Inc. 10590 West Ocean Drive, Suite 200 San Diego, CA 92130
Drug Name:	Omeprazole Immediate Release Powder for Oral Suspension (OSB-IR) 20 mg
Drug Class:	Proton-Pump Inhibitor
Proposed Indication:	Short-term Treatment of Active Duodenal Ulcer, Short-term Treatment and Maintenance of Erosive Esophagitis, Treatment of Heartburn and GERD
Documents Reviewed:	Consultation Response from Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety
Division Director:	Robert Justice, M.D., M.S.
Deputy Director:	Joyce Korvick, M.D., M.P.H.
Team Leader (Acting)	Ruyi He, M.D.
Medical Officer:	Lolita A. Lopez, M.D.

I. INTRODUCTION

Omeprazole is a proton-pump inhibitor (PPI) indicated for the short-term therapy of gastroesophageal reflux disease, gastric and duodenal ulcers, and gastric hypersecretory conditions including Zollinger-Ellison syndrome, systemic mastocytosis, and multiple endocrine adenomas. It is also used in the treatment of H. pylori infection in combination with clarithromycin and amoxicillin. It has a long duration of action and is very potent, allowing for once-daily administration. This drug was first approved in Europe in 1988 and in the United States in 1989. Generic omeprazole capsules were approved in November 2001.

Omeprazole is acid-labile and is rapidly degraded by gastric acid. It is available as Prilosec Delayed-Release Capsules containing enteric-coated omeprazole granules. Currently, all marketed PPIs taken orally are delivered with an enteric-coating to protect the drug from rapid degradation upon exposure to acid. This enteric coating makes these formulations to have delayed-release characteristics.

II. BACKGROUND

The sponsor, Santarus, Inc. is developing omeprazole sodium bicarbonate-immediate release (OSB-IR) 20 mg as an immediate-release omeprazole formulation that can be administered as a liquid. In this formulation, the enteric coating is replaced by sodium bicarbonate, whose primary role in the formulation is to neutralize gastric acid and protect omeprazole from gastric acid degradation, until it can be absorbed.

On November 20, 2002, the Division of Gastroenterology and Coagulation Drug Products (DGCDP) requested a tradename consult to the Division of Medication Errors and Technical Support (DMETS) for the sponsor's proposed proprietary names "Acitrel" / "Rapinex". DMETS does not recommend the use of either name because the Expert Panel identified the proprietary names: Acthrel, Acitretin, Actonel, Factrel, Accupril and Ovidrel as having potential for confusion with "Acitrel" and also identified the proprietary names: Repronex, Rapamune, Rheumatrex and Regranex as having potential for confusion with "Rapinex". See consultation response by Linda Wisniewski (DMETS) dated December 29, 2003.

III. RECOMMENDATION

From a clinical standpoint, this reviewer concurs with the recommendations of DMETS. The sponsor should propose other proprietary name(s) for this product.

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

/s/

Lolita Lopez
1/23/04 02:44:01 PM
MEDICAL OFFICER

Ruyi He
1/23/04 05:18:52 PM
MEDICAL OFFICER

CLINICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	**21-636**
Type of Submission:	**505(b)(2)**
Sponsor:	**Santarus, Inc.** **10590 West Ocean Air Drive, Suite 200** **San Diego, CA 92130**
Date Submitted:	**August 15, 2003**
Drug Name:	**Omeprazole-Immediate Release Powder for Suspension (OSB-IR) 20mg**
Drug Class:	**Proton-Pump Inhibitor**
Proposed Indication:	**Short-term Treatment of Active Duodenal Ulcer** **Treatment of Heartburn and other Symptoms Associated with Gastroesophageal Reflux Disease** **Short-term Treatment of Erosive Esophagitis** **Maintenance of Healing Erosive Esophagitis**
Documents Reviewed:	**Clinical Section of the NDA Volumes 1-3 (Electronic Submission)** **Prilosec® 20mg Capsules Package Insert**
Division Director:	**Robert Justice, M.D., M.S.**
Deputy Director:	**Joyce Korvick, M.D., M.P.H.**
Team Leader:	**Ruyi He, M.D.**
Medical Officer:	**Lolita A. Lopez, M.D.**
Biopharmaceutics:	**Suliman Al-Fayoumi, Ph.D.**
Chemist:	**Marie Kowblansky, Ph.D.**
Project Manager:	**Susan Daugherty, R.N., B.S.N.**

Table of Contents

Clinical Review for NDA 21-636

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Omeprazole Sodium Bicarbonate-Immediate Release Powder for Oral Suspension (OSB-IR) 20 mg is recommended to be approvable by this medical officer for the following indications:

- Short-term treatment of active duodenal ulcer (20 mg once a day for 4-8 weeks)
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD) (20 mg once a day up to 4 weeks)
- Short-term treatment of erosive esophagitis which has been diagnosed by endoscopy (20 mg once a day for 4-8 weeks)
- Maintenance of healing erosive esophagitis (20 mg once a day)

OSB-IR 20mg should be taken at least one hour before eating after emptying the contents of packet into a small cup containing 15-30 ml of water. It is for adult use only; there are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review (see Appendix B).

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

This new formulation, OSB-IR will provide a therapeutic benefit to the pediatric population; therefore, C

J, I recommend that the sponsor also conduct appropriate pediatric studies in children 2 to — years old as a Phase IV commitment.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Omeprazole is a proton-pump inhibitor which has been approved in the United States since 1989. It suppresses gastric acid secretion by specific inhibition of the H+/K+ adenosine triphosphatase (ATPase) enzyme system at the secretory

surface of the gastric parietal cell therefore blocking the final step of acid production.

Omeprazole is currently used for the treatment of acid-related gastrointestinal disorders such as short-term treatment of active duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), maintenance treatment of healing of erosive esophagitis, treatment of pathological hypersecretory conditions and H. pylori eradication (when used with clarithromycin and/or amoxicillin). It is also approved in children two years and older for the treatment of GERD and other acid-related disorders. It is currently available by prescription as 10mg, 20mg, and 40mg delayed release *capsules*. It is also available over-the-counter (OTC) as a 20mg omeprazole magnesium delayed release *tablet* indicated for the treatment of frequent heartburn.

Like other PPIs, omeprazole is acid-labile and is rapidly degraded by gastric acid. Current available omeprazole formulations are delivered with enteric-coatings as a protection from rapid degradation upon exposure to acid. This enteric-coating gives the drug its delayed-release characteristic.

In this submission, the sponsor seeks approval for a new immediate-release formulation, omeprazole sodium bicarbonate-immediate release powder for suspension (OSB-IR) 20mg that can be administered as a liquid. In this formulation, the enteric coating is replaced by sodium bicarbonate, whose primary role in the formulation is to neutralize gastric acid and protect omeprazole from gastric acid degradation, until it can be absorbed. Although the neutralization of gastric acid is a direct pharmacologic action of the antacid, the effect is transient and does not contribute to the therapeutic effect for chronic acid-related conditions that require continuous suppression of gastric acid for four to eight weeks or longer. No claim is being made regarding the therapeutic effect of sodium bicarbonate.

The sponsor relies on FDA's previous finding of safety and efficacy for omeprazole for the approval of OSB-IR and submits this NDA under a 505(b)(2) application. The sponsor conducted two bioequivalent studies comparing the pharmacokinetics (PK)/pharmacodynamics (PD) of OSB-IR Suspension and Prilosec® Delayed-Release Capsules (20 and 40 mg for both formulation) in a total of 70 healthy Subjects. OSB-IR CO6 enrolled 36 subjects (primary study reviewed) and OSB-IR CO2 enrolled 34 subjects (supportive study). The primary focus of the studies are the PK/PD results at steady state (7 days of consecutive single daily morning dosing). If the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials *would* provide a bridge from OSB-IR to Prilosec and to FDA's previous finding of safety and efficacy for omeprazole.

B. Efficacy

There are no new clinical efficacy trials that were submitted with this NDA. The efficacy of all PPIs is directly related to their ability to suppress gastric acid. Pharmacodynamic data can provide important supportive evidence of a drug's therapeutic effect. The bioequivalent study conducted by the sponsor have shown that the OSB-IR 20mg formulation and Prilosec® 20mg Delayed Release Capsules exhibited similar AUC values on both days 1 and 7. Using standard definitions of bioequivalence (mean ratios of test to reference and 90% CIs of 80% to 125%), OSB-IR 20 mg and Prilosec 20 mg were bioequivalent with respect to the primary PK/PD endpoints, AUC(0-inf) and percent decrease from baseline in 24-hour integrated gastric acidity on Day 7, respectively. The two treatments were not bioequivalent with regard to Cmax on either Day 1 or Day 7 with the entire 90% CI exceeding 125% on both days. This higher Cmax for OSB-IR 20 mg was anticipated as a result of eliminating the delayed-release coating of omeprazole. .

The higher Cmax for OSB-IR 20 mg is not expected to have any meaningful effect on the efficacy or safety of OSB-IR 20mg compared to Prilosec 20mg because this Cmax is below the Cmax for Prilosec 40mg which does not raise any safety concern.

All four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose and subsequently greater after the seventh dose for both treatments. The two omeprazole formulations showed similar levels of suppression for each of the four gastric acid parameters.

In addition, administration of OSB-IR 20mg one hour postmeal reduced AUC by 24% and Cmax by 63% relative to one hour pre-meal administration; therefore, this drug should be taken on an empty stomach at least one hour before meals.

Overall, the trials have shown that OSB-IR and Prilosec were a comparable in suppressing gastric acid secretion and provide support of therapeutic equivalence for OSB-IR 20mg and Prilosec® 20mg.

C. Safety

Omeprazole has been proven safe and effective in the U.S. for almost 15 years even at high doses (up to 120 mg three times a day); a 20mg omeprazole tablet is available for OTC use. It has been marketed worldwide since 1988 and over [ ] prescriptions has been written worldwide making it as one of the most frequently prescribed medications.

The combination of postmarketing data, previous clinical trials and adverse events analysis with the studies (OSB-IR-C06 and OSB-IR-C02) establish the safety of OSB-IR. OSB-IR 20mg was well tolerated up to eight consecutive daily doses. The percentages of subjects reporting at least one adverse event for the OSB-IR formulation were similar to the percentages for the omeprazole delayed capsule. The most commonly reported adverse events across the OSB trials are headache (7.5%); nausea and throat irritation (both 3.8%); and dizziness (2.5%).

This formulation contains sodium (460mg in the form of sodium bicarbonate); therefore, it should be taken with caution in patients on sodium restricted diet. In addition, this formulation contains 1680mg (20meq) of sodium bicarbonate; sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. It should also be used with caution in patients Bartter's syndrome, hypokalemia, respiratory alkalosis and those with problems with systemic acid-base balance. Further, long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome. Known adverse reactions (rate unknown) with sodium bicarbonate include: abdominal pain, flatulence, hypernatremia, metabolic alkalosis, peripheral edema, seizures, tetany, and tremor.

D. Dosing

Dose: Omeprazole Sodium Bicarbonate - Immediate Release, Powder for Suspension (OSB-IR) 20 mg

Indications:

- Short-term treatment (4-8 weeks) of active duodenal ulcer
  20 mg once a day
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
  20 mg once a day up to 4 weeks
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
  20 mg once a day for 4-8 weeks
- Maintenance of healing erosive esophagitis
  20 mg once a day

The current package insert for omeprazole states that *no* dosage adjustment is necessary for the elderly or patients with renal impairment. It also reports that no specific antidote for omeprazole overdosage is known. Treatment should be symptomatic and supportive. Overdosage up to 2400 mg (120 times the usual recommended clinical dose) have been reported. The manifestations included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone.

There was no data provided in this submission regarding dosage adjustment for omprazole containing sodium bicarbonate; however, due to the sodium and bicarbonate content of OSB-IR, caution should be used in patients who require fluid restriction, and those with problems with systemic acid-base balance. Overdose with sodium bicarbonate include hypocalcemia, hypokalemia, hypernatremia, and seizures.

D. Special Populations

Since this NDA only contains bioequivalent studies conducted in healthy patients, there are no new data regarding the effects of gender, race or age on safety or efficacy. The sponsor refers to the information in the current labeling of Prilosec®.

Pediatric

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population.

Geriatric

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population.

For omeprazole, no dosage adjustment is necessary in the elderly. Pharmacokinetic studies have shown the elimination rate in the elderly was somewhat decreased and bioavailability was increased. The plasma clearance of omeprazole was about half that of young volunteers and its plasma half-life was about twice that of young healthy volunteers. In clinical trials in the US and Europe, omeprazole was administered to over 2000 elderly individuals $\geq$ 65 years old. No differences in safety and effectiveness between the elderly and younger subjects were noted.

Chronic Hepatic Disease

In patients with chronic hepatic disease, the bioavailability of omeprazole increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect. The plasma half-life of the drug increased to nearly 3 hours compared.to the half-life in normal subjects; plasma clearance decreased.

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population.

Chronic Renal Impairment

In patients with chronic renal impairment (creatinine clearance of

10-62 mL/min/1.73 m^2) the disposition of omeprazole was very similar to that in healthy volunteers, with only a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population. No specific guidelines for sodium bicarbonate dosage adjustment is available in patients with renal impairment.

Race

In Asians, PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis.

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population.

Pregnancy Use

This application has no new information regarding pregnant women. Omeprazole and sodium bicarbonate are both currently listed as Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Caution is advised in regular use of sodium bicarbonate in pregnancy. Increased sodium intake during pregnancy can produce edema and weight increase.

Nursing Mothers

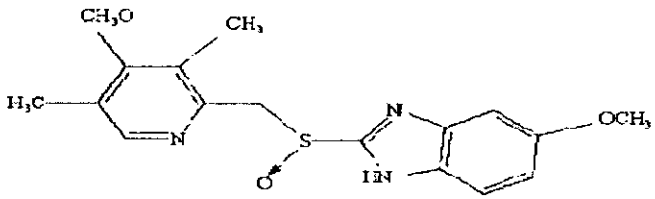
Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse effects, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug: Omeprazole Sodium Bicarbonate-Immediate Release Powder for Oral Suspension (OSB-IR) 20mg



Class: Proton-pump Inhibitor

Proposed Indications:

- Short-term treatment (4-8 weeks) of active duodenal ulcer
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
- Maintenance of healing erosive esophagitis

Regimen: Short-Term Treatment of Active Duodenal Ulcer
20 mg once daily (most patients heal within four weeks).

GERD with No Esophageal Lesions
20 mg daily for up to 4 weeks

GERD with Erosive Esophagitis
20 mg daily for 4 to 8 weeks

Maintenance of Healing of Erosive Esophagitis
20 mg daily.

Preparation and Administration of Suspension:

- OSB-IR 20mg should be taken at least one hour before eating.

- Contents of packet should be emptied into a small cup containing [1 of water. Stir well [1, and drink immediately. Refill cup with water and drink.

Age Group: Adults

B. State of Armamentarium for Indication(s)

There are five proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lanzoprazole and rabeprazole) approved for use in the United States. Proton pump inhibitors (PPIs) are unstable at a low pH. The oral dosage forms ("delayed release") are supplied as enteric-coated granules encapsulated in a gelatin shell (omeprazole and lansoprazole) or as enteric-coated tablets (pantoprazole and rabeprazole). The granules dissolve only at an alkaline pH, thus preventing degradation of the drugs by acid in the esophagus and stomach. Lansoprazole is supplied as a delayed-release oral suspension composed of enteric-coated granules.

Currently, none of the five PPIs has an immediate release action. The applicant is proposing immediate-release omeprazole formulation that can be administered as a liquid. In this formulation, the enteric coating is replaced by sodium bicarbonate, whose primary role in the formulation is to neutralize gastric acid and protect omeprazole from gastric acid degradation, until it can be absorbed. Although the neutralization of gastric acid is a direct pharmacologic action of the antacid, the effect is transient and does not contribute to the therapeutic effect for chronic acid-related conditions that require continuous suppression of gastric acid for four to eight weeks or longer.

C. Important Milestones in Product Development

Omeprazole was originally approved by the FDA in September 1989 for acute treatment only due to concern regarding long-term use. Thereafter, a study was published documenting the superiority of maintenance therapy for 12 months with omeprazole over ranitidine in patients with reflux esophagitis. In December 1994, FDA approved the use of omeprazole for maintenance therapy of healing erosive esophagitis. In April 1996, a 14-day regimen consisting of omeprazole and clarithromycin was approved for the treatment of H. pylori-associated duodenal ulcer; a 10-day regimen of omeprazole, amoxicillin, and clarithromycin was approved in June 1998. Generic omeprazole capsules were approved in November, 2001.

In July 2002, the FDA approved its use for children 2 years and older for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD and maintenance of healing of erosive esophagitis. A non-prescription omeprazole product was approved by the FDA on June 20, 2003;

Prilosec OTC™ (delayed-release omeprazole 20 mg) is indicated for the short-term treatment of frequent heartburn (2 or more episodes per week).

Dr. Michael Metzler from the University of Missouri submitted IND 46,656 on November 10, 1994 to study the use of a simplified omeprazole suspension (SOS) (omeprazole bicarbonate solution) in the prophylaxis of stress-related mucosal damage. In late 1995, Dr. Metzler began studying a flavored SOS (Chocobase) for pediatric gastroesophageal reflux disease (GERD). He then subsequently transferred ownership of this IND to Santarus, Inc. on January 31, 2001 for commercial development of simplified omperazole suspension.

On October 21, 2001, a meeting was held between the Agency and Santarus, Inc. discussing the clinical development plan for omeprazole sodium bicarbonate – immediate release (OSB-IR) powder for suspension. The sponsor proposed their plan to conduct a pharmacokinetic/pharmacodynamic (PK/PD) study comparing OSB-IR to the listed drug product, Prilosec (omeprazole) Delayed-Release Capsules and submit an NDA under a 505(b)(2) application.

The sponsor also expressed [redacted]

1 This will be submitted under a different NDA.

On August 8, 2003, Santarus, Inc. submitted NDA 21-626 for the approval of OSB-IR 20mg powder for suspension as an immediate-release omeprazole formulation that can be administered as a liquid.

D. Other Relevant Information

Omeprazole has been marketed worldwide under various trade names since 1988 and was first approved for marketing in the United States (US) in 1989. It is currently marketed under the trade name of Prilosec® in the US and has an excellent safety profile. Over 380 million prescriptions have been written worldwide to date making it as one of the most frequently prescribed medications.

E. Important Issues with Pharmacologically Related Agents

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. A new class labeling for PPIs was recently incorporated in the label regarding potential drug interactions with these drugs. The label also includes a statement regarding been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly.

When disulfiram is coadministered with a protein pump inhibitor, toxicity has been reported.[1] The most common adverse effects caused by PPIs are nausea, abdominal pain, constipation, flatulence, and diarrhea. Also reported are subacute myopathy, arthralgias, headaches, and skin rashes.
There are conflicting data on the risk and clinical implications of enterochromaffin-like cell hyperplasia in patients on long-term proton pump inhibitor therapy. PPIs have a track record of more than 15 years of use worldwide, and no major new issues regarding safety have emerged. There is as yet no reason to believe, therefore, that hypergastrinemia should be a trigger for discontinuation of therapy or that gastrin levels should be monitored routinely in patients on long-term proton pump inhibitor therapy. However, the development of a hypergastrinemic state may predispose the patient to rebound hypersecretion of gastric acid following discontinuation of therapy.[2]

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

In this 505(b)(2) application, the sponsor submitted PK and PD studies to bridge OSB-IR to Prilosec and to FDA's previous finding of safety and effectiveness for omeprazole by showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects. This NDA focuses on the use of OSB-IR 20mg (Trial OSB-IRCO6), therefore the information for the higher dose formulation (OSB-40mg) will be used as a supporting information. Dr. Suliman Al-Fayoumi from the Agency reviewed OSB-IR-C06 in detail. See Biopharm review for details.

No new animal or toxicology studies were submitted with this NDA. In the most recent package insert of omeprazole, animal studies in a two 24-month carcinogenicity studies in rats, omeprazole at daily doses of about 0.7 to 57 times human dose produced gastric ECL cell carcinoids in a dose-related manner. An increased incidence of ECL cell hyperplasia was observed in the treated group when compared to the control group over a two-year period. Gastric adenocarcinoma was seen in one rat (2%); this finding involving only one tumor is difficult to interpret. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

[1] GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS - 10th Ed. (2001) Online
[2] GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS - 10th Ed. (2001) Online

III. Human Pharmacokinetics and Pharmacodynamics

The sponsor submitted two pharmacokinetics (PK)/pharmacodynamics (PD) bioequivalence trials, OSB-IR-C06 (OSB-IR 20mg vs. Prilosec® 20mg Delayed-Release Capsules) and OSB-IR-C02 (OSB-IR 40mg vs. Prilosec® 40mg Delayed-Release Capsules). The primary focus of the studies are the PK/PD results at steady state (7 days of consecutive single daily morning dosing).

A. Pharmacokinetics

A Comparison of the PK/PD of OSB-IR 20 mg suspension and Prilosec® 20 mg Delayed-Release Capsules in Healthy Subjects showed that OSB-IR 20 mg was not bioequivalent to Prilosec capsule 20 mg. The two formulations exhibited similar omeprazole AUC values on both days 1 and 7, but substantial differences were observed between the two formulations on Cmax (around 60%), which would be anticipated given the differences in release rates between OSB-IR and Prilosec Delayed-Release Capsules.

Administration of OSB-IR 20mg one hour postmeal reduced AUC by 24% and Cmax by 63% relative to one hour pre-meal administration.

B. Pharmacodynamics

Dr. Al-Fayoumi commented that with regard to the PD findings, while there were some differences observed in the inhibition of acid secretion on day 1, the differences across all the determined PD parameters appeared to diminish by day 7, and that overall, OSB-IR appears to result in similar inhibition of acid secretion relative to Prilosec. See Biopharm review for details.

IV. Description of Clinical Data and Sources

A. Overall Data

Clinical Section of the NDA Volume 1 paper copy
NDA Electronic Submission
Package Insert Prilosec® Delayed Capsules
Orange Book
Pharmacology Online Monograph for sodium bicarbonate

B. Tables Listing the Clinical Trials

Table 1: Clinical Trials in Support of NDA 21-636

Type of Trial	*Trial Identifier*	*Objective*	*Design*	*Dosage and Administration*	*Subjects*	*Duration of Treatment*
Primary						
PK/PD	OSB-IR-C06	To compare PK/PD profiles of OSB-IR and Prilosec	Crossover (OSB-IR 20mg vs Prilosec 20mg)	OSB-IR 20mg suspension, q.d. 8 days or q.d. 7days and b.i.d. 1 day, oral	36 Healthy	OSB-IR-8days Prilosec-7 days.
Supportive						
PK/PD	OSB-IR-C02	To compare PK/PD profiles of OSB-IR and Prilosec	Crossover (OSB-IR 40mg vs Prilosec 40mg)	OSB-IR 40mg suspension, q.d. 7 days or q.d. 8 days oral	32 Healthy	OSB-IR-7 or 8 days Prilosec-7 days

C. Postmarketing Experience

Omeprazole has been marketed worldwide under various trade names since 1988 and was first approved for marketing in the United States (US) in 1989. It is currently marketed under the trade name of Prilosec® in the US. Omeprazole is one of the most frequently prescribed medications with over [ ] prescriptions written worldwide to date.

Omeprazole Sodium Bicarbonate-Immediate Release Powder for Suspension has not been approved nor marketed in any country.

D. Literature Review

The sponsor submitted a list of references/articles from peer reviewed journal and published articles. This reviewer has also searched the literature for information on omeprazole and sodium bicarbonate, and incorporated this information in the review.

V. Clinical Review Methods

A. How the Review was Conducted

The proposal for the use of a new immediate-release formulation, omeprazole sodium bicarbonate-immediate (OSB-IR 20mg) that can be administered as a liquid was based on a bioequivalent study, OSB-IR CO6, comparing OSB-IR 20mg and Prilosec 20mg delayed release capsules. The information for the higher

dose formulation (OSB-IR CO2:OSB-40mg)) has been used as a supporting information.

The primary focus of the review is study OSB-IR CO6.

C. Overview of Materials Consulted in Review

Clinical Section of the NDA Volume 1 paper copy
NDA Electronic Submission
Package Insert Prilosec® Delayed Capsules
Pharmacology Online
Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 9th ed. (Online)
Harrison's: Principles of Internal Medicine, 16th ed. (Online)
Drug Information Handbook, 8th ed.
Physicians' Desk Reference
Orange Book

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

A comprehensive review of OSB-IR CO6 bioequivalent study was performed. A DSI audit was conducted for this study and did not uncover any issues affecting the integrity of the data.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

This research was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the US 21 CFR Part 312.20 and the principles enunciated in the latest version of the Declaration of Helsinki.

E. Evaluation of Financial Disclosure

The applicant submitted an FDA form 3454 certifying that none of the investigators of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

There were no efficacy evaluations for this trial except for pharmacodynamic evaluations. By showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials provide a bridge from OSB-IR to Prilosec and to FDA's previous finding of safety and efficacy for omeprazole.

Two bioequivalent studies comparing the PK and PD profiles of OSB-IR and Prilosec at doses of 20 mg and 40 mg of omeprazole are included in this submission to support the indications proposed for inclusion in the OSB-IR 20 mg labeling. This NDA is for the use of OSB-IR 20mg; the information for the higher dose formulation (OSB-IR40mg) has been used as a supporting information.

The study have shown that the OSB-IR 20mg formulation and Prilosec® 20mg Delayed Release Capsules exhibited similar AUC values on both days 1 and 7. However, substantial differences were observed between the two formulations on Cmax (around 60% higher for OSB-IR), which would be anticipated given the differences in release rates between OSB-IR and Prilosec Delayed-Release Capsules. In addition, AUC and Cmax are reduced by 24% and 63%, respectively when OSB-IR is administered one hour postmeal relative to administration one hour pre-meal.

Overall, with regards to PD findings, OSB-IR 20mg appears to be comparable with regards to inhibition of acid secretion relative to Prilosec® Delayed Capsules 20mg. The efficacy of Prilosec (omeprazole) is related to its ability to suppress gastric acid; OSB-IR 20mg appears to be comparable to Prilosec with regards to inhibition of acid secretion. Therefore, the results of the studies provide an important evidence of OSB-IR's therapeutic effect.

B. General Approach to Review of the Efficacy of the Drug

Efficacy was assessed by utilizing the data submitted by the applicant comprising bioequivalent studies comparing OSB-IR 20 mg and Prilosec 20mg. By showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, it is deemed that the trials will provide a bridge from OSB-IR 20mg to Prilosec 20mg and to FDA's previous finding of safety and efficacy for omeprazole.

C. Detailed Review of Trials by Indication

A full summary and review of each of the trials is included in the appendix.

D. Efficacy Conclusions

In summary, a comparison of the PK/PD of OSB-IR 20 mg suspension and Prilosec® 20 mg Delayed-Release Capsules in healthy subjects was conducted to support the proposed indications, a similar study utilizing the 40mg dose for each formulation was also conducted and was reviewed as a supportive study for the 20mg dose.

Using standard definitions of bioequivalence (mean ratios of test to reference and 90% CIs of 80% to 125%), OSB-IR 20 mg and Prilosec 20 mg were bioequivalent with respect to the primary PK/PD endpoints, AUC(0-inf) and percent decrease from baseline in 24-hour integrated gastric acidity on Day 7, respectively. OSB-IR 20 mg had a higher Cmax on days 1 and 7 with the entire 90% CI exceeding 125% on both days. This difference in Cmax could be anticipated given the differences in release rates between OSB-IR and Prilosec Delayed-Release Capsules. In addition, AUC and Cmax are reduced by 24% and 63%, respectively when OSB-IR is administered one hour postmeal relative to administration one hour pre-meal.

The studies have shown that all four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose and greater after the seventh dose for both OSB-IR and Prilosec. Each of the four gastric acid parameters mentioned above showed similar levels of suppression for the two omeprazole formulations.

Although PD data are not regarded by the Agency to be of equal importance as clinical data in support of efficacy for OSB-IR, PK/PD data is regarded as supportive of the clinical data because clinical symptoms and outcome of acid related disorders are directly related to acid output . Overall, the trials have shown that OSB-IR and Prilosec were comparable in suppressing gastric acid secretion and provide support of therapeutic equivalence for OSB-IR 20mg and Prilosec® 20mg.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Omeprazole has been proven safe and effective in the U.S. for almost 15 years even at high doses (up to 120mg three times a day); a 20mg omeprazole tablet is available for OTC use. The combination of postmarketing data, previous clinical trials and adverse events analysis with these studies: OSB-IR-C06 (primary) and OSB-IR-C02 (supportive) establish the safety of OSB-IR.

OSB-IR 20mg and 40mg were well tolerated up to eight consecutive daily doses. The percentages of subjects reporting at least one adverse event for the OSB-IR formulation were similar to the percentages for Prilosec®. The most commonly reported adverse events across these OSB trials (OSB-IR C06 and C02) are headache (7.5%); nausea and throat irritation (both 3.8%); and dizziness (2.5%). There were no deaths in these trials. One patient discontinued the from the trial due to a moderate adverse event which was not related to the trial drug.

The higher Cmax for OSB-IR 20 mg is not expected to have any meaningful effect on the efficacy or safety of OSB-IR 20mg compared to Prilosec 20mg because this Cmax is below the Cmax for Prilosec 40mg which does not raise any safety concern.

It should be kept in mind that this formulation contains 1680 mg (20meq) of sodium bicarbonate; 460mg sodium in the form of sodium bicarbonate, therefore, it should be taken with caution in patients on sodium restricted diet. Further, sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. It should also be used with caution in patients with Bartter's syndrome, hypokalemia, and respiratory alkalosis. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome. Known adverse reactions (rate unknown) from sodium bicarbonate use include: abdominal pain, flatulence, hypernatremia, metabolic alkalosis, peripheral edema, seizures, tetany, lactic acidosis and tremor.

B. Description of Patient Exposure

A total of 70 healthy adult subjects were enrolled in these two randomized, crossover, bioequivalent studies comparing OSB-IR and Prilosec®. Subjects who received at least one dose of the trial drug were included in the safety analysis. A total of 68 subjects received one dose of the trial drug and therefore included in the safety analysis. A total of 66 subjects (OSB-IRCO6=35; OSB-IRCO2=31) completed the trial.

In the OSB-IRCO6 trial, 18 (50%) of the subjects received eight doses of OSB-IR 20 mg and 18 (50%) of the subjects received nine doses of OSB-IR 20 mg. A total of 35 (97%) subjects received seven consecutive daily doses of Prilosec 20 mg. One subject (#34), who did not return for Period 2, received eight doses of OSB-IR 20 mg, but did not receive any doses of Prilosec 20 mg.

In the OSB-IRCO2 trial, 16 (50%) of the subjects received eight doses of OSB-IR 40 mg and 15 (47%) of the subjects received seven doses of OSB-IR 40 mg. A total of 31 (97%) subjects received seven doses of Prilosec 40 mg. One subject (# 3), discontinued the trial because of an AE; received seven doses of Prilosec and only six doses of OSB-IR. One subject (#6) missed the third dose of Prilosec thus received eight doses of OSB-IR and six doses of Prilosec.

C. Methods and Specific Findings of Safety Review

Omeprazole is already approved as safe and efficacious, has been marketed worldwide under various trade names since 1988 and in the US since 1989. It is one of the most frequently prescribed medications with over [ ] prescriptions written worldwide to date. The safety experience for Prilosec® has

been up to high doses (360mg per day). Omeprazole (Prilosec OTC®) has also been approved for over the counter use since June 2003.

Two studies were reviewed in this submission to assess the bioequivalence of OSB-IR and Prilosec® (20 & 40mg). None of these trials was conducted specifically to assess safety issues with this immediate-release formulation of omeprazole. The following table shows the treatment emergent adverse event for trials OSB-IR-C06 and OSB-IR-C02. Table 2 shows the number (%) of subjects dosed with OSB-IR with adverse events by body system.

Table 2: Number (%) of Subjects Dosed with OSB-IR with Adverse Events by Body System

	OSB-IR-C06 (n = 36)		OSB-IR-C02 (n = 32)	
MedDRA Body System Preferred Term	**OSB-IR 20 mg N (%)**	**Prilosec 20 mg N (%)**	**OSB-IR 40 mg N (%)**	**Prilosec 40 mg N (%)**
Overall	**7 (19.4)**	**6 (16.7)**	**8 (25.0)**	**6 (18.8)**
Ear and labyrinth disorders	**0**	**0**	**1 (3.1)**	**0**
Ear pain	0	0	1 (3.1)	0
Eye disorders	**0**	**0**	**1 (3.1)**	**0**
Eye pruritus	0	0	1 (3.1)	0
Gastrointestinal disorders	**2 (5.6)**	**1 (2.8)**	**3 (9.4)**	**3 (9.4)**
Abdominal pain upper	1 (2.8)	0	1 3.1)	0
Constipation	0	0	0	1 (3.1)
Lip dry	0	1 (2.8)	0	0
Loose stools	0	0	1 (3.1)	0
Nausea	0	0	1 (3.1)	2 (6.3)
Throat irritation	1 (2.8)	0	1 (3.1)	1 (3.1)
Infections and infestations	**0**	**0**	**1 (3.1)**	**1 (3.1)**
Otitis media NOS	0	0	1 (3.1)	0
Pharyngitis viral NOS	0	0	0	1 (3.1)
Injury, poisoning and procedural complications	**0**	**0**	**0**	**1 (3.1)**
Joint sprain	0	0	0	1 (3.1)
Nervous system disorders	**3 (8.3)**	**3 (8.3)**	**2 (6.3)**	**2 (6.3)**
Dizziness	0	0	0	0
Headache NOS	1 (2.8)	1 (2.8)	2 (6.3)	2 (6.3)
Paraesthesia	0	1 (2.8)	0	0
Sinus headache	0	1 (2.8)	0	0
Somnolence	1 (2.8)	0	0	0
Vasovagal attack	1 (2.8)	0	0	0
Respiratory, thoracic and mediastinal disorders	**4 (11.1)**	**2 (5.6)**	**1 (3.1)**	**0**
Epistaxis	0	1 (2.8)	1 (3.1)	0
Nasal passage irritation	1 (2.8)	0	0	0
Pharyngitis	2 (5.6)	0	0	0
Sinus congestion	1 (2.8)	0	0	0
Sneezing	0	1 (2.8)	0	0
Skin and subcutaneous tissue	**0**	**1 (2.8)**	**3 (9.4)**	**0**

disorders				
Dry skin	0	0	2 (6.3)	0
Pruritus NOS	0	0	1 (3.1)	0
Rash NOS	0	1 (2.8)	0	0
Skin nodule	0	0	1 (3.1)	0

Adapted from sponsor's electronic submission, summary p.124-125

Table 3: Number (%) of Subjects Dosed with OSB-IR with Adverse Events by Body System and Relationship to Trial Drug (Trials: OSB-IR-C06, OSB-IR-C02)

	OSB-IR-C06 (n = 36)				OSB-IR-C02 (n = 32)			
	OSB-IR 20 mg		Prilosec 20 mg		OSB-IR 40 mg		Prilosec 40 mg	
MedDRA Body System	**NR N (%)**	**R N (%)**	**NR N (%)**	**R N (%)**	**NR N (%)**	**R N (%)**	**NR N (%)**	**R N (%)**
Overall	**6 (17)**	**1 (3)**	**3 (8)**	**3 (8)**	**6 (19)**	**2 (6)**	**4 (13)**	**2 (6)**
Ear and labyrinth disorders	0	0	0	0	1 (3)	0	0	0
Eye disorders	0	0	0	0	1 (3)	0	0	0
Gastrointestinal disorders	2 (6)	0	1 (3)	0	2 (6)	1 (3)	2 (6)	1 (3)
Infections and infestations	0	0	0	0	1 (3)	0	1 (3)	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1 (3)	0
Nervous system disorders	2 (6)	1 (3)	1 (3)	2 (6)	1 (3)	1 (3)	1 (3)	1 (3)
Respiratory, thoracic and mediastinal disorders	4 (11)	0	2 (6)	0	1 (3)	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	1 (3)	3 (9)	0	0	0

Adapted from sponsor's electronic submission, summary p.126

The denominator for calculating percentages is the number of intent-to-treat subjects in each trial.
Bolded entries indicate AEs considered related to OSB-IR.
R-related or possible NR-not related or unlikely

E. Adequacy of Safety Testing

This is a 505(b)(2) submission. For the trials in this NDA, the sponsor performed the appropriate safety monitoring for the subjects.

F. Summary of Critical Safety Findings and Limitations of Data

Overall, OSB-IR 20mg appears safe to use for the proposed indications. The trials reviewed were bioequivalence studies lasting only for up to eight days. It is expected that this drug will be used for a longer period than it was studied. The sponsor conducted an 8-week open-label trial (OSB-IR-C07) to assess the safety of OSB-IR 40mg administered daily for 8 weeks to patients with acid related conditions. The final report will be submitted to the Agency by May 2004.

Due to the sodium bicarbonate (1680mg) content of this formulation, it should be used with caution in patients who are sodium restricted problems and patients who have problems with systemic acid-base balance. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia.

VIII. Dosing, Regimen, and Administration Issues

Dose:

Omeprazole Sodium Bicarbonate - Immediate Release, Powder for Suspension (OSB-IR) 20 mg

Indications:

- Short-term treatment (4-8 weeks) of active duodenal ulcer
  20 mg once a day
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
  20 mg once a day up to 4 weeks
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
  20 mg once a day for 4-8 weeks
- Maintenance of healing erosive esophagitis
  20 mg once a day

OSB-IR Oral Suspension should be taken at least one hour before eating.
It is available as 20 mg single dose packets.

Directions for use: Empty packet contents into a small cup containing [ ] water. Do not use other liquids or foods. Stir well [ ] and drink immediately. Refill cup with water and drink.

No dosage adjustment is needed in the elderly. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis. PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians.

IX. Use in Special Populations

The trials included in this NDA are bioequivalence studies conducted in healthy patients; therefore, there are no new data regarding the effects of gender, race or age on safety or efficacy. The sponsor refers to the information in the current labeling of Prilosec®.

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

No new data regarding gender effects were submitted with this submission. There are no known differences in efficacy or safety based on gender with the use of omeprazole.

In this study conducted by the sponsor, the majority of subjects were males (83%) with some females (17%); the population was too small to give additional information.

C. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There are no new data concerning the effect of *age* or *race* on safety and efficacy with the use of omeprazole were submitted this application. In the Prilosec® package insert, it is reported that in Asians, PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis.

In this study, 72% of the subjects were Hispanics, and there was only one subject of Asian Indian descent.

C. Evaluation of Pediatric Program

No data regarding pediatric population were included in this submission.
The sponsor anticipates [redacted]

[redacted] In pediatric patients who are 2 years and older, the sponsor would like to reference the Agency's previous finding of safety and efficacy for Prilosec as described in its label at the time the pediatric exclusivity for that information expires (January 12, 2006).

This new formulation, OSB-IR will provide a therapeutic benefit to the pediatric population; therefore, [redacted]

I recommend that the sponsor also conduct appropriate pediatric studies in children 2 to [redacted] years old as a Phase IV commitment.

D. Comments on Data Available or Needed in Other Populations

Omeprazole has been used widely in the pediatric and geriatric population. No dosage adjustment is necessary when used in the elderly. Prilosec® is labeled for use in children as young as two years old. There is no available liquid omeprazole formulation for these patients. At this time, data in patients younger than two years old is needed and will be greatly beneficial especially to patients with gastroesophageal reflux.

Due to the sodium bicarbonate content of OSB-IR, additional data in the renally impaired and in patients with acid-base imbalance will be informative.

X. Conclusions and Recommendations

A. Conclusions

A comparison of the PK/PD of OSB-IR 20 mg suspension and Prilosec® 20 mg Delayed-Release Capsules in healthy subjects (OSB-IR CO6) was conducted to support the following indications: short-term treatment of active duodenal ulcer, GERD (with and without esophageal lesions) and maintenance of healing erosive esophagitis. The trials provide a bridge from OSB-IR to Prilosec and to FDA's previous finding of safety and efficacy for omeprazole.

In this proposed new immediate-release omeprazole formulation, OSB-IR 20mg, omeprazole can be administered as a liquid. The enteric coating is replaced by sodium bicarbonate, whose primary role in the formulation is to neutralize gastric acid and protect omeprazole from gastric acid degradation, until it can be absorbed. Although the neutralization of gastric acid is a direct pharmacologic action of the antacid, the effect is transient and does not contribute to the therapeutic effect for chronic acid-related conditions that require continuous suppression of gastric acid for four to eight weeks or longer. No claim is being made regarding the therapeutic effect of sodium bicarbonate.

A Comparison of the PK/PD of OSB-IR 20 mg suspension and Prilosec® 20 mg Delayed-Release Capsules in Healthy Subjects showed that the two formulations exhibited similar omeprazole AUC values on both days 1 and 7. Differences were observed between the two formulations on Cmax (around 60%), which would be anticipated given the differences in release rates between OSB-IR and Prilosec Delayed-Release Capsules. In addition, administration of OSB-IR 20mg one hour postmeal reduced AUC by 24% and Cmax by 63% relative to one hour pre-meal administration.

All four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose and subsequently greater after the seventh

dose for both treatments. The two omeprazole formulations showed similar levels of suppression for each of the four gastric acid parameters.

The combination of postmarketing data, previous clinical trials with Prilosec® Delayed Release Capsules and adverse events analysis with these studies (OSB-IR-C06 and OSB-IR-C02) establish the safety of OSB-IR. OSB-IR 20mg was well tolerated up to eight consecutive daily doses.

OSB-IR formulation will benefit patients who prefer liquid to a solid dosage form or who are unable to swallow a capsule such as the neurologically impaired and the elderly.

B. Recommendations

From a clinical standpoint, the bioequivalent studies submitted by the applicant revealed that OSB-IR 20mg appears to be comparable to Prilosec® Delayed Release Capsule 20 mg in inhibiting acid secretion. This supports the approval of OSB-IR 20mg for use in short-term treatment of active duodenal ulcer, GERD (with and without esophageal lesions) and maintenance of healing erosive esophagitis.

Although PD data is not as important as clinical data in support of efficacy, PD biomarkers (intragastric pH and intraesophageal pH) are relevant surrogate markers in acid-related gastrointestinal conditions. Therefore, I recommend that omeprazole sodium bicarbonate-immediate release (OSB-IR) powder for suspension be approvable for the proposed indications.

In addition, it should be noted that this formulation contains sodium bicarbonate as an excepient, and although the sponsor does not claim any therapeutic effect for this, caution should be exercised when administering OSB-IR 20mg to patients who require fluid restriction and to patients who have problems with acid-base balance. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Patients and clinicians should be made aware that this formulation contains 1680mg sodium bicarbonate. It also contains 460 mg of sodium in the form of sodium bicarbonate. This should be addressed on the product's label.

This new formulation, OSB-IR will provide a therapeutic benefit to the pediatric population; therefore, [redacted]

] I recommend that the sponsor also conduct appropriate pediatric studies in children 2 to [redacted] years old as a Phase IV commitment.

The sponsor should incorporate the labeling changes proposed in my labeling review in the Appendix section.

XI. Appendix

APPENDIX A
(Individual More Detailed Study Reviews)

Clinical Trial: OSB-IR-C06

A Comparison of the Pharmacokinetics and Pharmacodynamics of Omeprazole Sodium Bicarbonate-Immediate Release (OSB-IR) 20 mg Suspension and Prilosec® 20 mg Delayed-Release Capsules in Healthy Subjects

Clinical Phase I

Study Period: September 27, 2002 to November 12, 2002

Objectives

Primary:

- To test the hypothesis that OSB-IR 20 mg is pharmacokinetically bioequivalent to Prilosec 20 mg.

Secondary:

- To assess if OSB-IR 20 mg is pharmacodynamically bioequivalent to Prilosec 20 mg
- To compare the pharmacokinetics of OSB-IR 20 mg administered postmeal to the pharmacokinetics of OSB-IR 20 mg administered premeal
- To evaluate the effect of a second dose of OSB-IR 20 mg (ie, bedtime dose) on nocturnal gastric acidity

Study Design

A randomized, crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of seven consecutive daily doses of OSB-IR 20 mg compared to Prilosec 20 mg in healthy subjects. A comparison of pharmacokinetic parameters for OSB-IR administered before versus after a meal was also conducted.

Volunteers were screened within 14 days before baseline measurements (ie, gastric pH, vital signs). Gastric pH was recorded for 24 hours before the first dose of trial drug. In Period 1, subjects received OSB-IR 20 mg or Prilosec 20 mg, as randomized, 1 hour before breakfast for seven consecutive days. Blood samples to determine plasma omeprazole concentrations were collected for 12 hours and gastric pH levels were measured for 24 hours after the dose on Days 1 and 7.

On Day 8, subjects who had received OSB-IR 20 mg in Period 1 were given an eighth dose 1 hour after the start of breakfast. Blood samples were collected for 12 hours after the eighth dose. After a 10- to 14-day washout period, subjects returned for Period 2 and received the alternate treatment from that received in Period 1. Procedures in Period 2 were identical to those in Period 1 except for Day 8.

On Day 8 of Period 2, subjects who had received OSB-IR in Period 2 were administered an eighth dose after the completion of the 24-hour monitoring period after Dose 7 and 1 hour before beginning a standardized breakfast. After this eighth dose, subjects remained at the trial center and were served standardized meals at 1300 and 1800 hours (approximately 5 and 10 hours, respectively, after the eighth dose); no other food was consumed on Day 8. At 2200 hours, subjects were administered a second OSB-IR 20 mg dose (Dose 9). These subjects remained at the trial site for a total of 24 hours after Dose 8 with continuous pH monitoring.

Table 1: Times and Events Table

Procedure	Screen Visit	Period 1 (a)			Period 1 (Dosing) (a)								Period 2 (a)			Period 2 (Dosing) (a)							
		Baseline (b)			1st Dose (b)			7th Dose (b)			8th Dose Meal (c)		Baseline (d)			1st Dose(d)			7th Dose(d)			8th/9th Doses (e)	
Days (D)	D(-14)	D0	D1	D2	D0	D1	D2	D6	D7	D8	D8	D9	D0	D1	D2	D0	D1	D2	D6	D7	D8	D8	D9
Informed Consent	X																						
Review Entry Criteria	X	X			X			X					X			X			X				
Medical History	X																						
Physical Examination	X																				X		X
Vital Signs (f)	X		X	X		X	X		X	X		X		X	X		X	X		X	X		X
Clinical Laboratory Tests	X(g,h,i)	X(h)			X(h,i)			X(h,i)					X(h)			X(h,i)			X(h,i)		X(g)		X(g)
Esophageal Manometry (j)	X																						
Check-In		X			X			X					X			X			X				
Administer Test Article (k)						X	X	X	X		X						X	X	X	X		X	
Meals (l)			X			X			X		X(c)			X			X			X		X(e)	
Blood Samples						X(m)			X(m)		X(n)						X(m)			X(m)			
Gastric pH Begin	X(o)		X(p)			X(q)			X(q)					X(p)			X(q)			X(q)		X(r)	
Gastric pH End				X			X			X					X			X			X		X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Checkout				X			X			X		X			X			X			X		X

Adapted from sponsor's electronic submission TrialOSB-IR CO6 p.22

a Initiation of the Screening Visit and of Period 1 were separated by 1 - 14 days. The screening procedures occurred over several days. Period 1 baseline and dosing segments were separated by 2–10 days. Ten to 14 days for washout were required from the last dose in Period 1 to the first day of baseline of Period 2.

b Period 1 included visits for evaluation of baseline 24-hour gastric pH and 24-hour gastric pH and plasma omeprazole levels after Dose 1 (Day 1) and Dose 7 (Day 7).

c Subjects who had received OSB-IR in Period 1 remained in the clinic and continued for Dose 8 of OSB-IR on Day 8 administered at the completion of the 24-hour monitoring period after Dose 7. Dose 8 was administered 1 hour after initiation of a standardized breakfast. The breakfast was eaten over a 30-minute period. Following Dose 8, pharmacokinetics, only, were evaluated during the first 12 hours postdose in the clinic. Standardized meals were ingested (each within a 30-minute interval) at 5 and 10 hours after the eighth dose.

d Period 2 (baseline and Dose Days 1-7) procedures were the same as Period 1, but evaluated the omeprazole formulation alternative to that evaluated in Period 1 (by randomization).

e Subjects who had received OSB-IR in Period 2 remained in the clinic and continued for Dose 8 of OSB-IR on Day 8 administered (between 0800 and 0900) 1 hour prior to initiation of a standardized breakfast. The breakfast was eaten over a 30-minute period. Following Dose 8, pharmacodynamics only were evaluated during the 24 hours postdose in the clinic. Standardized meals were ingested (each within a 30-minute interval) at 1300 and 1800 hours after the eighth dose. Dose 9 was administered at 2200 hours.

f Vital signs (pulse, oral temperature, respiratory rate, sitting blood pressure) were measured at Screening, before Baselines, before Doses 1 and 7, and before checkouts.

g Hematology and serum chemistries. Laboratory tests were performed on specimens taken at the Screening Visit and on Day 8 (or Day 9 if subject received OSB-IR) of Period 2. A blood sample (10 mL) was collected at the Screening Visit for possible genotyping.

h Urine drug and alcohol screening were performed at Screening Visit and at check-ins for all overnight clinic visits.

i Pregnancy testing was performed at Screening and at overnight check-ins (Day 0 and Day 6) for each dosing segment for each trial period.

j At the Screening Visit, the nasogastric pH probe was inserted and the location of the upper border of the lower esophageal sphincter (LES) was made using manometry.

k Doses 1 and 7 in Periods 1 and 2 were administered in the trial clinic and subjects remained in clinic for the 24-hour postdose periods. For daily Doses 2 through 6, for each trial period, subjects were administered these in the morning in the trial clinic after an overnight fast and were observed for 1 hour (fasting, no water) and then released. Subjects were then allowed to consume food and drink per protocol.

l For dose Days 1 and 7, standardized meals were eaten at 1, 5 and 10 hours postdose (ie, after test article or water for baseline).

m Blood samples (5 mL) were taken just prior to dosing, and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) after dosing on Days 1 and 7.

n Blood samples (5 mL) were taken just prior to the meal initiation, and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) after dosing.

o The pH probe was placed 10 cm below the upper border of the LES and the pH had to be <2.5. The inserted probe had to be tolerated by the subject for at least 15 minutes at the Screening Visit.

p For baseline evaluations, a volume of 120 mL of water was administered 1 hour after initiating pH monitoring. Continuous pH monitoring occurred from 1 hour prior to, through 24 hours after water administration.

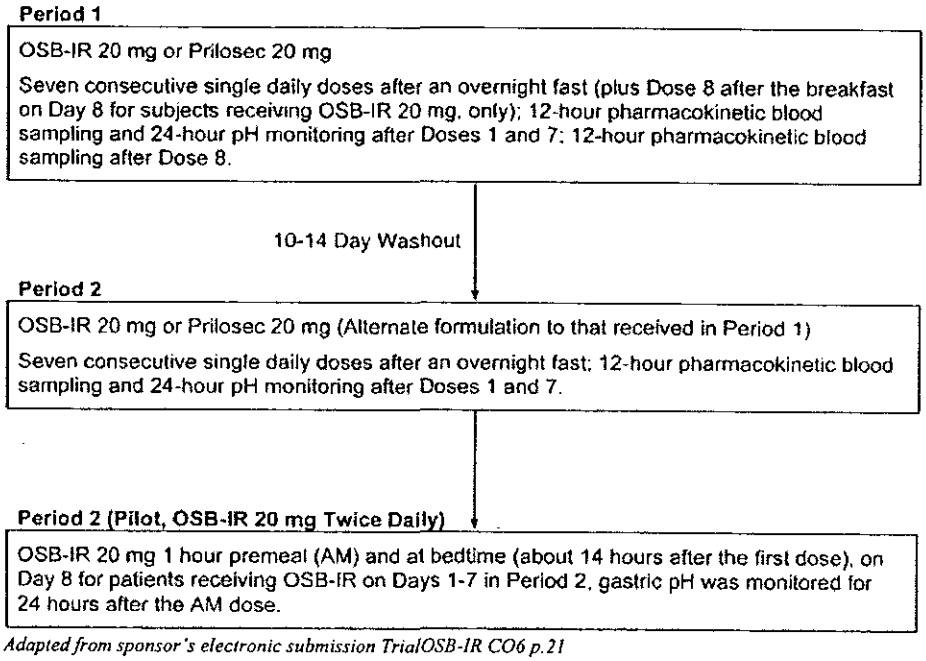
q For Days 1 and 7 dosing segments, continuous pH monitoring occurred from 1 hour before dosing through 24 hours after dosing.

r For Period 2, Days 8 and 9, continuous pH monitoring occurred from approximately ½ hour before Dose 8 through 24 hours after this dose.

The following laboratory tests were conducted on samples collected:

Blood Chemistry	Hematology	Urine
Albumin	Hematocrit	Amphetamines
Alkaline phosphatase	Hemoglobin	Benzodiazepines
β-HCG	CBC with differential	Cocaine
Blood urea nitrogen (BUN)	Platelet count	Ethanol
Creatinine		Opiates
Alanine aminotransferase (ALT)		Tetrahydrocannabinol
Aspartate transaminase (AST)		
Total bilirubin		
Total protein		

Figure 1: Trial Flow Diagram



Adapted from sponsor's electronic submission TrialOSB-IR CO6 p.21

Treatments

A	OSB-IR 20 mg, overnight fast, 1 hour premeal	OSB-IR 20mg orally as a 20ml aqueous susp followed by 100ml water each morning, 1 hr before breakfast
B	Prilosec 20mg overnight fast, 1 hour premeal	Prilosec 20mg orally with 120ml water each morning, 1 hr before breakfast

Dose 8	OSB-IR 20 mg, 1 hr postmeal	OSB-IR 20mg orally as a 20ml aqueous susp, followed by 100ml water on Day 8 in Period 1 1hr after breakfast
Dose 8/9 (2x-daily dosing)	OSB-IR 20 mg, 1 hour premeal (AM) and bedtime	OSB-IR 20mg orally as a 20ml aqueous susp, followed by 100ml water on Day 8 in Period 2 1hr before breakfast and at bedtime (approx 14hrs after Dose 8)

The randomization of treatment sequences was generated by [ ] using statistical analysis system (SAS®) to provide a ratio of 1:1 for treatment sequences (AB:BA) and included randomizations for 36 subjects. The random number generator used was the SAS function RANUNI.

Study Population

Thirty-six subjects were enrolled to ensure that at least 24 subjects completed the trial: 36 were dosed and 35 completed the trial; 35 were included in the pharmacokinetic analysis and 28 were included in the pharmacodynamic analyses for Doses 1 and 7.

Inclusion Criteria

- Non-Asian subjects, either male or nonlactating, nonpregnant females who were postmenopausal, sterile, or using an acceptable birth control method.
- 18 to 45 years of age.
- Weight between 120 and 200 pounds and within ± 20% of their ideal body weight.
- Could tolerate installation of nasogastric pH probe and had a pH < 2.5 at Screening
- Had signed an approved informed consent form.
- Were in good health on the basis of history, physical examination, and laboratory values.
- Had not used any form of tobacco (e.g., smoking, chewing) for the last year.
- Could swallow a tablet or capsule without difficulty.

Exclusion Criteria

- Previously participated in a Santarus-sponsored trial and received any omeprazole formulation (to avoid introducing data bias into the trial).
- Any significant history of/or concurrent gastrointestinal diseases or conditions, such as GERD, heartburn, reflux esophagitis, peptic ulcer disease (gastric or duodenal), or a family history of peptic ulcer disease, gastric surgery.
- Significant medical history or concurrent illness, such as respiratory, allergic, psychiatric, neurological, renal, hepatic, cardiovascular, metabolic or endocrine condition, or any other medical condition that the investigator or medical monitor considered sufficiently serious to interfere with the conduct, completion, or

results of this trial or constituted an unacceptable risk to the subject.

- History of significant drug allergy.
- Hypersensitivity to any of the ingredients in the test articles.
- Positive urine test for alcohol or other drugs at any trial visit.
- Had taken any gastric antisecretory drugs (eg, H2-receptor antagonists or PPIs), antacids, or other prescription or over-the-counter (OTC) medications within 14 days prior to Period 1 or during the trial.
- Ingested foods or beverages that contained xanthine (eg, coffee, tea, chocolate) within 48 hours of entering the clinic for each trial period.
- Ingested grapefruit juice within 7 days of dose administration in any trial period.
- Donated blood or blood products within 30 days of entering the trial.
- Treated with any investigational drug or therapy or participated in a clinical trial in the 30 days prior.
- Any condition that could interfere with assessments, pose additional risks in administration of the trial drug to the subject, or preclude completion of the trial including a history of noncompliance, alcoholism, or drug abuse.
- Laboratory test result deviating by more than 20% from the normal reference ranges of the local laboratory, if the investigator judged the abnormality to be of possible clinical significance.
- Evidence of infection with HIV or carrier of hepatitis B surface antigen or hepatitis C antibody.

Concomitant Therapy

Subjects were not allowed to use any prescription or OTC medications (except birth control) throughout this trial. Any use of concomitant medications could have resulted in the subject's termination from this trial. In the event that a subject used a concomitant medication, the investigator was to contact the Santarus, Inc. monitor to discuss whether the subject should be discontinued. All concomitant medications were recorded in the CRF.

Withdrawal of Subjects

Subjects were discontinued from participation for the following reasons:

- Any abnormal clinical laboratory values resulting in the investigator's decision that allowing the subject to continue in the trial would be ill-advised.
- Use of unapproved concomitant medications.
- Occurrence of intolerable AEs.
- Withdrawal of consent by subject ("personal").
- Noncompliance with protocol.
- Development of an intercurrent illness, injury, or medical condition likely to interfere with subject safety, the overall assessment, or the required administration of trial medication.

- Development of any condition for which the investigator felt treatment withdrawal was justified.
- Termination of the trial by the sponsor.

If a subject was discontinued from the trial, the following procedures were to be performed:

- Perform a physical examination
- Collect blood for clinical laboratory analysis (including pregnancy testing)
- Record any AEs and medications since the previous visit
- Complete End of Treatment Status CRF

Safety

Safety assessments throughout this trial consisted of physical examination, vital signs measurements, monitoring for use of concomitant medications and clinical laboratory testing. A pregnancy test [serum β-HCG] was performed on samples taken from females at the screening visit and at each admission into the clinic site monitoring for adverse events. Results from pregnancy testing and urine alcohol and drug screens were reviewed before the next dose of trial drug was administered.

Adverse Events

The intensity, duration, and relationship to treatment of AEs and the use of concomitant medications were evaluated. Changes from baseline in physical examination findings, vital sign measurements, and clinical laboratory test results were evaluated. All adverse events were recorded on the CRF during the trial even if the AE was assessed by the investigator as unlikely to be causally related to trial drug treatment.

The investigator was required to notify Santarus of any SAE by SAE Fax Form if an event occurred within 30 days after a subject had completed treatment in this clinical trial and if such event was judged to be probably or possibly related to test article.

Details of any AEs that occurred were collected during each trial period. After the subject had an opportunity to spontaneously mention any problems, the investigator or assigned staff inquired about AEs by asking the following standard questions:
At clinic check-ins:

1. "Have you had any medical problems since your last visit?"
2. "Have any medical problems present at your last visit changed, i.e., stopped, worsened, or improved?"
3. "Have you taken any medicines, other than trial drug, since your last visit?"

Efficacy

There were no efficacy measurements in this trial.

Pharmacokinetic Endpoints:

Primary
The bioavailability of omeprazole area under the plasma drug concentration curve calculated from 0 time and extrapolated to infinity [AUC(0-inf)] after the seventh dose of each omeprazole formulation.

Secondary

- Peak plasma concentration (Cmax) after the seventh dose of each omeprazole formulation
- AUC(0-inf) after the first dose of each omeprazole formulation
- All other pharmacokinetic parameters after the first and seventh doses of each omeprazole: formulation: Time at which Cmax is observed (Tmax), elimination rate constant (kel), half-life of drug elimination (T½), area under the plasma drug concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)]
- All pharmacokinetic parameters obtained with OSB-IR 20 mg administered postmeal

Pharmacodynamic Endpoints:

Primary
The percent decrease from baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation.

Secondary

- Percent decrease from baseline in mean gastric acid concentration and percent time gastric pH was ≤ 4, and the increase from baseline in median gastric pH for the 24-hour interval after the seventh dose of each omeprazole formulation
- Percent decrease from baseline in integrated gastric acidity, mean gastric acid concentration, and in the percent time gastric pH was ≤ 4 and the increase from baseline in median gastric pH for the 24-hour interval after the first dose of each omeprazole formulation
- Median gastric pH and the percent time gastric pH was ≤ 4 after 24-hour interval after dosing on Days 7 and 8 in Period 2 for OSB-IR

Pharmacokinetic Sampling, Analytical Methods, and Parameters

Blood samples (5 mL) were to be obtained by venipuncture within 30 minutes before the dose and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) after the dose on Days 1 and 7 of both

periods and Day 8 of Period 1. Zero time was the time that the subject swallowed a capsule or the first 20 mL of liquid formulation of trial drug.

Plasma omeprazole concentrations were measured using a previously validated liquid chromatography mass spectrometry (LC-MS/MS) assay. The assay range was [ ] ng/mL.

The following pharmacokinetic parameters were evaluated:

- Plasma omeprazole concentration at each sampling time
- Peak plasma concentration (Cmax) and the time at which Cmax is observed (Tmax) obtained directly from the data without interpolation
- Elimination rate constant (kel) determined from a log-linear regression analysis of the terminal plasma omeprazole concentrations
- Half-life of drug elimination (T½) calculated as ln2/kel (using kel calculated for each respective period and dose)
- Area under the plasma drug concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)] calculated using the trapezoidal rule with the plasma concentration at time "t" being the last measurable concentration
- Area under the plasma drug concentration curve calculated from 0 time and extrapolated to infinity [AUC(0-inf)] calculated as AUC(0-t) + Ct/kel, where Ct is the last measurable plasma concentration (using kel calculated for each respective period and dose)

Pharmacodynamic Parameters and Methodology

The following pharmacodynamic parameters were evaluated for each 24-hour period in 15-minute intervals:

- Integrated gastric acidity, calculated as follows:
  - Acid concentration (mM) = 1000 x 10-pH
  - Acidity (mmol* hr/L)= (acid in mM at time "t"+ acid in mM at time "t-1")/2 x (t – t-1)
  - Integrated gastric acidity expressed as mM x time, ie, mmol* hr/L
- Mean gastric acid concentration: calculated as 4 x integrated acidity for the 15-minute interval
- Median gastric pH
- Percent time gastric pH ≤ 4

Statistical Methods

Safety parameters were summarized by treatment using descriptive statistics and included subjects who received at least one dose of trial drug.

Pharmacokinetics:

Pharmacokinetic parameters were evaluated using standard criteria for bioequivalence. A parametric (normal-theory) general linear model was applied to the logarithmic transformations of the area under the plasma drug concentration curve (AUC) and Cmax values. The 90% confidence intervals (90% CIs) for treatment differences (OSB-IR 20 mg vs Prilosec 20 mg) were calculated for log-transformed AUC and Cmax. These confidence intervals were then reverse transformed and multiplied by 100 to represent confidence intervals about the treatment mean ratios on a percentage scale. Analysis of variance (ANOVA) was also applied to the same parameters to evaluate differences in the pharmacokinetics of omeprazole when OSB-IR 20 mg was given before and after a meal. The 90% CIs for treatment mean ratios (postmeal:premeal) were calculated.

Pharmacodynamics:

Pharmacodynamic parameters were evaluated using the standard methodology for bioequivalence. Baseline values for all pharmacodynamic parameters were first compared between the two treatment periods using an ANOVA model. If there were no statistically significant differences in baseline values for any parameter, the baseline values for the two periods were averaged when calculating change from baseline; otherwise, the corresponding baseline value for that period was used. Using an ANOVA model, 90% CIs were calculated for the ratio of treatment means (OSB-IR 20 mg / Prilosec 20 mg) on the natural log-transformed scale. These confidence intervals were then reverse transformed.

Ethics

This research was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the US 21 CFR Part 312.20 and the principles enunciated in the latest version of the Declaration of Helsinki.

Results

Patient Characteristics

Table 2: Demographic Summary for All Subjects

Trait		Female	Male	Overall
Sex (N)	Female	6	0	6
	Male	0	30	30
Race (N)	Black	1	0	1
	Caucasian	2	6	8
	Hispanic	3	23	26
	Other (Asian Indian Descent)	0	1	1
Frame Size (N)	Small	0	10	10
	Medium	3	19	22
	Large	3	1	4
Age (years)	Mean	33	29	30
	SD	9	6	7
	Minimum	20	19	19
	Maximum	44	45	45
	N	6	30	36
Weight (pounds)	Mean	142.8	163.0	159.6
	SD	6.7	18.7	18.8
	Minimum	132.0	134.0	132.0
	Maximum	152.0	197.0	197.0
	N	6	30	36
Height (inches)	Mean	63.8	67.1	66.6
	SD	2.5	3.0	3.1
	Minimum	61.0	62.0	61.0
	Maximum	67.0	74.0	74.0
	N	6	30	36

Adapted from electronic submission TrialOSB-IR CO6 p.39

Medical Officer Comments: The majority of subjects were males (83%) and Hispanics comprised 72% of the subjects. The mean age was 30 years with age range from 19 to 45 years. There appears to be no clinically significant differences in the demographic or baseline characteristics (medical histories, physical findings, vital signs) between the females and males participating in this trial.

The sponsor enrolled only one Asian in the trial. A higher percentage of Asians compared to Caucasians are poor metabolizers of omeprazole, and the differing PK profiles might confound trial results (see Prilosec Prescribing Information – Clinical Pharmacology section).

Patient Accounting

Thirty-six subjects entered the trial and received at least one dose of trial drug; 35 subjects completed the trial. Subject 34 failed to return for Period 2 procedures and was lost to follow up thereafter.

Pharmacokinetic Results

The pharmacokinetic parameters of omeprazole for Days 1 and 7 are presented in the following tables.

Table 3: Summary of Day 1 (Premeal) Plasma Omeprazole Pharmacokinetic Parameters for OSB-IR 20 mg and Prilosec 20 mg

	Plasma Omeprazole							
	OSB-IR 20 mg			Prilosec 20 mg				
Parameters*	N**	Arithmetic Mean	SD	N**†	Arithmetic Mean	SD	% Mean Ratio ‡	90% CI for % Mean Ratio
Cmax (ng/mL)	35	671.9	294.5	35	461.5	289.9	-	-
Tmax (hr)	35	0.50	0.33	35	1.74	1.11	-	-
AUC (0-t) (ng*hr/mL)	35	816.2	591.8	35	867.1	678.3	-	-
AUC (0-inf) (ng*hr/mL)	35	825.4	593.5	33	903.4	697.4	-	-
T ½ (hr)	35	0.86	0.29	33	1.21	0.66	-	-
kel (1/hr)	35	0.90	0.28	33	0.70	0.30	-	-
ln (Cmax)	35	6.42	0.44	35	5.95	0.64	160.44	140.41 - 183 33
ln [AUC(0-t)]	35	6.52	0.61	35	6.54	0.68	97.80	91.71 - 104.29
ln [AUC(0-inf)]	35	6.53	0.60	33	6.58	0.68	95.90	89.97 - 102.23

Adapted from sponsor's electronic submission TrialOSB-IR CO6 p41

* Values for Cmax, AUC(0-t), and AUC(0-inf) are rounded to four significant figures and all other parameters are rounded to two decimal points after statistical analyses are performed.

** Subject 34 is excluded from the analysis because the statistical analysis plan indicated that only subjects completing both 7-day treatment periods would be included.

† Subject 3 is not included in the analyses of AUC(0-inf) and ln[AUC(0-inf)] because kel could not be calculated since there was no clear log-linear decline in plasma omeprazole concentrations.

‡ % Mean Ratio = 100 * exp(OSB-IR - Prilosec); based on least-squares means.

Medical Officer Comments: The above table shows that both OSB-IR 20mg and Prilosec 20mg were bioequivalent with respect to AUC(0-inf) but not to Cmax after one dose.
The Cmax for OSB-IR 20 mg was higher than for Prilosec 20 mg (mean ratio 160.44%, 90% CI of 140.41 to 183.33%). The mean Tmax value for OSB-IR was shorter (0.5 hr) than the Tmax value for Prilosec (1.74 hr), [p < 0.001].

Table 4: Summary of Day 7 (Premeal) Plasma Omeprazole Pharmacokinetic Parameters for OSB-IR 20 mg and Prilosec 20 mg

	Plasma Omeprazole							
	OSB-IR 20 mg			Prilosec 20 mg				
Parameters*	N**	Arithmetic Mean	SD	N**†	Arithmetic Mean	SD	% Mean Ratio‡	90% CI for % Mean Ratio
Cmax (ng/mL)	35	902.2	357.1	35	573 1	225.1	-	-
Tmax (hr)	35	0.47	0.18	35	1.39	0.49	-	-
AUC (0-t) (ng*hr/mL)	35	1434	869.8	35	1302	733.7	-	-
AUC (0-inf) (ng*hr/mL)	35	1446	875.8	34	1351	729.2	-	-
ln (Cmax)	35	6.72	0.45	35	6.26	0.46	157.02	141.50 - 174.24
ln [AUC(0-t)]	35	7.07	0.67	35	7.00	0.62	107.21	100.76 - 114.07
ln [AUC(0-inf)]	**35**	**7.09**	**0.67**	**34**	**7.07**	**0.56**	**106.71**	**100.01 - 113.86**

Adapted from sponsor's electronic submission Trial OSBIR CO6p.42

* Values for Cmax, AUC(0-t), and AUC(0-inf) are rounded to four significant figures and all other parameters are rounded to two decimal points after statistical analyses are performed.

** Subject 34 is excluded from the analysis because the statistical analysis plan indicated that only subjects completing both 7-day treatment periods would be included

† Subject 3 is not included in the analyses of AUC(0-inf) and ln[AUC(0-inf)] because kel could not be calculated since there was no clear log-linear decline in plasma omeprazole concentrations.

‡ % Mean Ratio = 100 * exp(OSB-IR - Prilosec); based on least-squares means.

Note: Primary pharmacokinetic endpoint was ln[AUC(0-inf)] on Day 7.

Medical Officer Comments: The table above shows that OSB-IR 20 mg and Prilosec 20 mg administered once daily premeal were bioequivalent with respect to AUC(0-inf). The least-squares means ratio was 106.71% with a 90% CI of within 80% and 125% (ie, 100.01% - 113.86%). The Cmax for OSB-IR 20 mg at steady state was greater than Prilosec 20 mg (mean ratio of 157.02%, 90% CI of 141.50% to 174.24%). The Tmax for OSB-IR was shorter than that of Prilosec (0.47 hr vs. 1.39 hr), ($p < 0.001$).

Table 5: Summary of OSB-IR 20 mg Postmeal (Day 8) vs OSB-IR 20 mg Premeal (Day 7) Plasma Omeprazole Pharmacokinetic Parameters at Steady State

	Plasma Omeprazole							
	OSB-IR 20 mg (Postmeal)			OSB-IR 20 mg (Premeal)				
Parameters*	N**	Arithmetic Mean	SD	N**	Arithmetic Mean	SD	% Mean Ratio‡	90% CI for % Mean Ratio
Cmax (ng/mL)	18	371.0	231.9	18	926.4	389.6	-	-
Tmax (hr)	18	1.07	0.59	18	0.51	0.18	-	-
AUC (0-t) (ng*hr/mL)	18	1304	999.2	18	1665	1165	-	-
AUC (0-inf) (ng*hr/mL)	18	1322	1016	18	1683	1185	-	-
ln (Cmax)	18	5.73	0.64	18	6.73	0.52	36.91	31.41 - 43.37
ln [AUC(0-t)]	18	6.90	0.80	18	7.18	0.76	75.56	70.57 - 80.90
ln [AUC(0-inf)]	18	6.91	0.79	18	7.19	0.76	76.08	71.07 - 81.45

Adapted from sponsor's electronic submission TrialOSB-IR CO6 p.43

* Values for Cmax, AUC(0-t), and AUC(0-inf) are rounded to four significant figures and all other parameters are rounded to two decimal points after statistical analyses are performed.

** All subjects who received Dose 8 of OSB-IR 20 mg after a meal in Period 1 are included in the analysis.

‡ % Mean Ratio = 100 * exp(postmeal - premeal); based on least-squares means.

Medical Officer Comments: Ingestion of OSB-IR 20 mg one hour after a standardized high-fat breakfast lowered the bioavailability to 76.08% [percent mean ratio (postmeal:premeal) for AUC(0-inf)]. The Cmax of was lowered to 36.91% (percent mean ratio) relative to premeal administration and the mean Tmax was delayed by 0.56 hours (34 minutes).

Pharmacodynamic Results

Subjects 20, 26, 27, 28, 32, 33, 34, and 36 did not qualify for pharmacodynamic analyses because they did not have all six acceptable pH records (ie, Baseline and Days 1 and 7 for each of the two periods).

Table 6: Cumulative Integrated Gastric Acidity (mmol* hr/L) with OSB-IR 20 mg and Prilosec 20 mg

Assessment	Integrated Gastric Acidity (mmol* hr/L)		OSB-IR/Prilosec (%)
	OSB-IR 20 mg	Prilosec 20 mg	By-Subject Ratios
Baseline			
Period 1	3386	4079	
	(2954 - 4084)	(2641 - 4390)	
Period 2	4523	3393	
	(3353 - 4999)	(2774 - 4802)	
Day 1			
Period 1	2253	2040	
	(1199 - 2604)	(1339 - 3719)	
Period 2	2376	1665	
	(949 - 2916)	(1275 - 2616)	
Day 7			
Period 1	961	762	
	(98 - 1192)	(164 - 1299)	
Period 2	717	837	
	(152 - 966)	(58 - 1208)	
Percent Decrease from Baseline* to:			
Day 1	46	46	103
	(28 - 65)	(26 - 58)	(47 - 163)
Day 7	**82**	**78**	**100**
	(73 - 96)	**(69 - 96)**	**(94 - 108)**

Adapted from sponsor's electronic submission TrialOSB-IR CO6 p.50

Note: Cumulative integrated gastric acidity is calculated for each 24-hour recording period for each of the 28 subjects.

The median decrease for both OSB-IR 20 mg and Prilosec 20 mg integrated gastric acidity was 46%. On Day 7, the corresponding median decreases were 82% and 78%, respectively. The median of the by-subject ratios (OSB-IR 20 mg/Prilosec 20 mg) of the decrease from baseline of integrated gastric acidity was 100%.

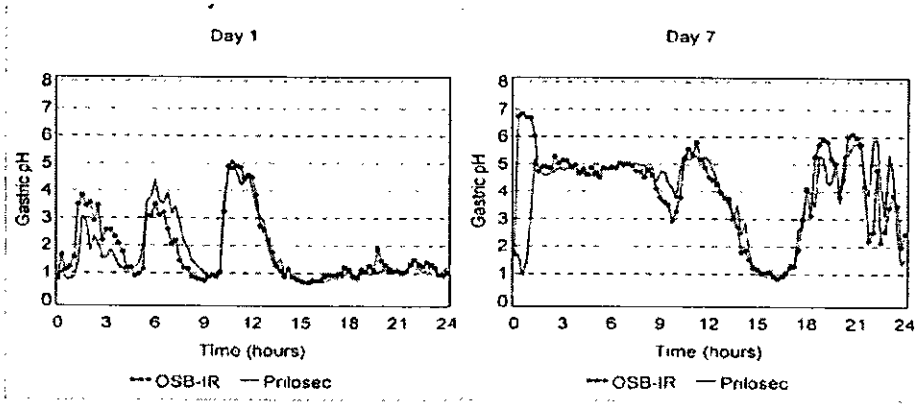
Table 7: Mean Gastric Acid Concentration (mM) with OSB-IR 20 mg and Prilosec 20 mg

Assessment	Mean Gastric Acid Concentration (mM)	
	OSB-IR 20 mg	Prilosec 20 mg
Baseline		
Period 1	141 (123 - 170)	170 (110 - 183)
Period 2	193 (140 - 208)	141 (116 - 200)
Day 1		
Period 1	94 (50 - 108)	85 (56 - 155)
Period 2	99 (40 - 121)	69 (53 - 109)
Day 7		
Period 1	40 (4 - 50)	32 (7 - 54)
Period 2	30 (6 - 40)	35 (2 - 50)

Adapted from sponsor's electronic submission TrialOSB-IR CO6 p.53

Note: The mean gastric acid concentration for the 24-hour recording period is obtained by dividing the 24-hour cumulative integrated gastric acidity for each subject by 24. Table entries present the medians and the boundaries of the interquartile range (25th and 75th percentiles) for these values by trial day and period.

Figure 2: Median Gastric pH with OSB-IR 20 mg and Prilosec 20 mg on Days 1 and 7



Adapted from sponsor's electronic submission Trial OSB-IR CO6 p.57

Note: Each time point represents a 15-minute interval. The value for zero (0) time is the value for the 15-minute interval just prior to the time of dosing. Values are displayed as medians for each 15-minute interval over the 24-hour recording period. Results are from 28 subjects.

The above figure shows that on Day 1, there was a slight increase in median gastric pH on the first hour after dosing with OSB-IR likely due to the neutralization of gastric acid by the sodium bicarbonate in OSB-IR. On day 1, there was also a greater increase in gastric pH after breakfast with OSB-IR than with Prilosec, and

the reverse after lunch. No difference in pH profile between the two treatments was noted after dinner.

On Day 7, the pH profiles of OSB-IR and Prilosec were the same, except during the first hour after dosing where an increase in median gastric pH to nearly 7 was observed only after OSB-IR administration.

Table 8: Percent Time Gastric pH ≤ 4 with OSB-IR 20 mg and Prilosec 20 mg at

Assessment	Percent Time Gastric pH ≤ 4	
	OSB-IR 20 mg	Prilosec 20 mg
Baseline		
Period 1	96	97
	(85 - 98)	(90 - 98)
Period 2	98	91
	(92 - 99)	(81 - 98)
Day 1		
Period 1	82	83
	(66 - 93)	(66 - 93)
Period 2	82	77
	(63 - 91)	(63 - 92)
Day 7		
Period 1	56	47
	(13 - 62)	(21 - 54)
Period 2	44	48
	(18 - 54)	(10 - 64)

Adapted from sponsor's electronic submission Trial OSB-IR ICO6 p58

Note: The percent time gastric pH ≤ 4 is calculated for each 24-hour recording period for each of the 28 subjects. Table entries present the medians and the boundaries of the interquartile range (25th and 75th percentiles) of these values by trial day and period.

Medical Officer Comments: On Day 1, the median percent time that gastric pH was ≤ 4 was similar for OSB-IR and Prilosec. For period 1 of day 7, the median percent time that gastric pH was ≤ 4 was slightly higher for OSB-IR (56%) than for Prilosec (47%). There was considerable intersubject variability for both products on Day 7.

Discussion

Clinical Trial OSB-IR-C06 is a comparison of the pharmacokinetics (PK) and pharmacodynamics (PD) of Omeprazole Sodium Bicarbonate-Immediate Release (OSB-IR) 20 mg Suspension and Prilosec® 20 mg Delayed-Release Capsules in Healthy Subjects. A total of 36 subjects were enrolled; 34 completed the trial. The majority of subjects were males (83%); 72% of the subjects were Hispanics. The mean age was 30 years with age range from 19 to 45 years. Only one Asian was enrolled due to a higher percentage of poor metabolizers and differing PK profiles in this population.

Both OSB-IR 20mg and Prilosec 20mg were bioequivalent with respect to AUC(0-inf) but not to Cmax after *one* dose (day 1). The Cmax for OSB-IR 20 mg was higher than for Prilosec 20 mg (mean ratio 160.44%, 90% CI of 140.41 to 183.33%).

The mean Tmax value for OSB-IR was shorter (0.5 hr) than for Prilosec (1.74 hr), [p < 0.001].

OSB-IR 20 mg and Prilosec 20 mg administered once daily on day 7 premeal were bioequivalent with respect to AUC(0-inf). The least-squares means ratio was 106.71% with a 90% CI of within 80% and 125% (i.e., 100.01% - 113.86%). The Cmax for OSB-IR 20 mg at steady state was greater than Prilosec 20 mg (mean ratio of 157.02%, 90% CI of 141.50% to 174.24%). The Tmax for OSB-IR was shorter than that of Prilosec (0.47 hr vs. 1.39 hr), (p < 0.001).

OSB-IR 20 mg taken one hour after a standardized high-fat breakfast lowered the bioavailability to 76.08% [percent mean ratio (postmeal:premeal) for AUC(0-inf)]. The Cmax of was lowered to 36.91% (percent mean ratio) relative to premeal administration and the mean Tmax was delayed by 0.56 hours (34 minutes).

On day 1, the median decrease for both OSB-IR 20 mg and Prilosec 20 mg integrated gastric acidity was 46%; on Day 7, the corresponding median decreases were 82% and 78%, respectively. The median of the by-subject ratios (OSB-IR 20 mg/Prilosec 20 mg) of the decrease from baseline of integrated gastric acidity was 100%.

On Day 1, there was a slight increase in median gastric pH on the first hour after dosing with OSB-IR likely due to the neutralization of gastric acid by the sodium bicarbonate in OSB-IR. On day 1, there was also a greater increase in gastric pH after breakfast with OSB-IR than with Prilosec, and the reverse after lunch. No difference in pH profile between the two treatments was noted after dinner.
On Day 7, the pH profiles of OSB-IR and Prilosec were the same, except during the first hour after dosing where an increase in median gastric pH to nearly 7 was observed only after OSB-IR administration.

On Day 1, the median percent time that gastric pH was ≤ 4 was similar for OSB-IR and Prilosec. For period 1 of day 7, the median percent time that gastric pH was ≤ 4 was slightly higher for OSB-IR (56%) than for Prilosec (47%). There was considerable intersubject variability for both products on Day 7.

In summary, using standard definitions of bioequivalence (mean ratios of test to reference and 90% CIs of 80% to 125%), OSB-IR 20 mg and Prilosec 20 mg were bioequivalent with respect to the primary PK/PD endpoints, AUC(0-inf) and percent decrease from baseline in 24-hour integrated gastric acidity on Day 7, respectively. However, these two treatments were not bioequivalent with regard to Cmax on either Day 1 or Day 7 with the entire 90% CI exceeding 125% on both days. The higher Cmax for OSB-IR 20 mg was expected as a result of eliminating the delayed-release coating.

All four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose and subsequently greater after the seventh dose for both treatments. In addition, each of the four gastric acid parameters showed similar levels of suppression for the two omeprazole formulations.

Safety

Subjects who received at least one dose of trial drug were included in the safety analysis. A total of 18 (50%) subjects received eight doses of OSB-IR 20 mg (consecutive daily doses) and 18 (50%) subjects received nine doses of OSB-IR 20 mg (eight consecutive daily doses and a second dose on the eighth day). Thirty-five (97%) of the subjects received seven consecutive daily doses of Prilosec 20 mg. Subject 34, did not return for Period 2, received eight doses of OSB-IR 20 mg, and did not receive any doses of Prilosec 20 mg.

Adverse Events

Below is a table for treatment-emergent AEs.

Table 9: Number (%) of Subjects with Adverse Events by Treatment Group

MedDRA Body System Preferred Term	OSB-IR 20 mg n = 36 N (%)	Prilosec 20 mg n = 35 N (%)	Total n = 36 N (%)
Number of Subjects with at least one AE	7 (19)	6 (17)	10 (28)
Gastrointestinal disorders			
Abdominal pain upper	1 (3)	0 (0)	1 (3)
Lip dry	0 (0)	1 (3)	1 (3)
Throat irritation	1 (3)	0 (0)	1 (3)
Nervous system disorders			
Headache NOS	1 (3)	1 (3)	2 (6)
Paraesthesia	0 (0)	1 (3)	1 (3)
Sinus headache	0 (0)	1 (3)	1 (3)
Somnolence	1 (3)	0 (0)	1 (3)
Vasovagal attack	1 (3)	0 (0)	1 (3)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	0 (0)	1 (3)	1 (3)
Nasal passage irritation	1 (3)	0 (0)	1 (3)
Pharyngitis	2 (6)	0 (0)	2 (6)
Sinus congestion	1 (3)	0 (0)	1 (3)
Sneezing	0 (0)	1 (3)	1 (3)
Skin and subcutaneous tissue disorders			
Rash NOS	0 (0)	1 (3)	1 (3)

Adapted from sponsor's electronic submission TrialOSB-IR CO6 p.37

A total of 7 (19%) subjects in the OSB-IR 20mg group and 6 (17%) in the Prilosec 20mg group experienced at least one AE. The intensity of AEs experienced by

subjects were mild, except for Subject 6 who had vasovagal attack, in Period 2 (moderate AE).

Subject 6 was reported to have had a blood pressure of 75/40 mmHg and pulse of 37 beats per minute (bpm) 21 hours after the seventh dose of OSB-IR 20 mg in Period 2. This episode of low blood pressure coincided with a vasovagal attack. Blood pressure increased to 131/77 mmHg 30 minutes later and the pulse increased to 59 bpm 3 hours later. The event was considered to be not related to the trial drug by the investigator.

Vital signs were otherwise similar in subjects receiving OSB-IR 20 mg and Prilosec 20mg.

There was no laboratory abnormality that was reported as an AE or any shifts or trends in any laboratory parameters during the trial.

The chemistry and hematology test results of several subjects were slightly above or below the normal ranges. These abnormalities were considered by the investigator to be not clinically significant in the context of this trial except for Subject 18 who received Prilosec 20 mg in Period 2,who thereafter had an elevated alanine aminotransferase of 79 U/L (normal range=0-50 U/L) and total bilirubin of 1.5 mg/dL (normal range=0.1– 1.1 mg/dL). This did not resolve at subsequent testing.

There were no clinically significant changes from baseline in the physical findings during this trial except for an adverse event for subject 4 who had normal findings during the physical examination at screening, but presented with a mild, bilateral erythema papular rash on the inner thighs at the end of Period 2.

OSB-IR 20 mg administered up to nine doses over 8 days were well tolerated by the subjects this trial.

Deaths

There were no deaths, serious AEs or other significant AEs reported during this trial.

Clinical Trial: OSB-IR-C02

Title of Trial: Comparison of the Pharmacokinetics and Pharmacodynamics of 40 mg Omeprazole Sodium Bicarbonate-Immediate Release (OSB-IR) Suspension and Prilosec® Delayed-Release Capsules in Healthy Subjects

Clinical Phase I

Study Period: May 10, 2002 to July 8, 2002

Objectives

Primary *Pharmacokinetic* Objective:

- To test the hypothesis that OSB-IR is bioequivalent to Prilosec at steady state with regard to area under the plasma drug concentration curve calculated from time zero to infinity [AUC(0-inf)] after the seventh consecutive daily dose of each omeprazole formulation.

Secondary *Pharmacokinetic* Objectives:

- To assess whether OSB-IR is equivalent to Prilosec with regard to peak plasma concentration (Cmax) after the seventh dose of each omeprazole formulation.
- To test the hypothesis that OSB-IR is bioequivalent to Prilosec after the first dose of each omeprazole formulation.
- To compare all the pharmacokinetic parameters obtained at steady state with OSB-IR administered premeal with those obtained with OSB-IR administered postmeal.

Primary *Pharmacodynamic* Objective:

- The primary pharmacodynamic objective was to assess whether OSB-IR is equivalent to Prilosec with regard to decreasing integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation.

Secondary *Pharmacodynamic* Objectives:

- To compare OSB-IR to Prilosec with respect to mean gastric acid concentration, median gastric pH, and the percent time gastric pH ≤ 4 for the 24-hour interval after the *seventh dose* of each omeprazole formulation.
- To compare OSB-IR to Prilosec with respect to the integrated gastric acidity, mean gastric acid concentration, median gastric pH, and the percent time gastric pH ≤ 4 for the 24-hour interval after the *first dose* of each omeprazole formulation.
- To compare OSB-IR to Prilosec with respect to the percent decrease from baseline in integrated gastric acidity, mean gastric acid concentration, the percent time gastric pH ≤ 4, and the percent increase from baseline in median gastric pH for the 24-hour interval after the first dose of each omeprazole formulation, expressed as a percentage of the corresponding value for the 24-hour interval after the seventh dose of each omeprazole formulation.

Study Design

A randomized, crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of seven consecutive daily doses of OSB-IR 40 mg compared to Prilosec 40 mg in healthy subjects. A comparison of pharmacokinetic parameters for OSB-IR administered before versus after a meal was also conducted.

Volunteers were screened within 14 days before baseline procedures (ie, gastric pH, vital signs). Gastric pH was recorded for 24 hours before the first dose of trial drug. In Period 1, subjects received OSB-IR 40 mg or Prilosec 40 mg, as randomized, 1 hour before breakfast for seven consecutive days. A standardized high-fat breakfast was given to subjects on Days 1 and 7 in the clinic. Blood samples to determine plasma omeprazole concentrations were collected for 12 hours and gastric pH levels were measured for 24 hours after the dose on Days 1 and 7.

On Day 8, subjects who received OSB-IR in Period 1 were given an eighth dose 1 hour after the start of the standardized high-fat breakfast. Blood samples were collected for 12 hours. After a 10- to 14-day washout period, subjects returned for Period 2 and received the alternate treatment from that received in Period 1. Procedures in Period 2 were identical to those in Period 1 except that Day 8 procedures were not conducted. See Times and Events Table.

Table 1: Times and Events Table

	Pre-Period 1(a)	Period 1(a)			Period 1 (Dosing) (a)						Period 1(a)		Period 2(a)			Period 2 (Dosing) (a)					
Procedure	Screening Visit(c)	Baseline(b)			Dose 1(b)			Dose 7(b)			Dose 8 (Fed)(d)		Baseline(c)			Dose 1(c)			Dose 7(c)		
Days (D)	D(-14)	D0	D1	D2	D0	D1	D2	D6	D7	D8	D8	D9	D0	D1	D2	D0	D1	D2	D6	D7	D8
Informed Consent	X																				
Review Entry Criteria	X	X			X			X					X			X			X		
Medical History	X																				
Physical Examination	X																				X
Vital Signs(e)	X		X	X		X	X		X	X	X	X		X	X		X	X		X	X
Clinical Laboratory Tests	X(f,g,h)	X(g)			X(g,h)			X(g,h)					X(g)			X(g,h)			X(g,h)		X(f)
Esophageal Manometry(i)	X																				
Check-In		X			X			X					X			X			X		
Administer Trial Drug(j)						X	X		X		X						X	X		X	
Meal (k)			X			X			X		X(d)			X			X			X	
Blood Samples						X(l)	X(l)		X(l)	X(l)	X(m)	X(m)					X(l)	X(l)		X(l)	X(l)
Gastric pH Begin(n)	X(n)		X(o)			X(p)			X(p)					X(o)			X(p)			X(p)	
Gastric pH End				X			X			X					X			X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Checkout				X			X			X		X			X			X			X

Adapted from sponsor's electronic submission TrialOSB-IR CO2 p. 22

a Initiation of the Screening Visit and of Period 1 were separated by 1-14 days. The screening procedures occurred over several days. Period 1 baseline and dosing segments were separated by 2–10 days. Ten to 14 days for washout were required from the last dose in Period 1 to the first day of baseline of Period 2.

b Period 1 included visits for evaluation of baseline 24-hour gastric pH and 24-hour gastric pH and plasma omeprazole levels after Dose 1 (Day 1) and Dose 7 (Day 7).

c Period 2 was the same design as Period 1, but evaluated the omeprazole formulation alternative to that evaluated in Period 1 (by randomization).

d Subjects who had received OSB-IR in Period 1 remained in the clinic and continued for Dose 8 of OSB-IR on Day 8 administered at the completion of the 24-hour monitoring period after Dose 7. Dose 8 was administered 1 hour after initiation of a standardized breakfast. The breakfast was eaten over a 30-minute period. Following Dose 8, only pharmacokinetic parameters were evaluated during the first 24 hours postdose in the clinic. Standardized meals were ingested (each within a 30-minute interval) at 5 and 10 hours after the eighth dose.

e Vital signs (pulse, oral temperature, respiratory rate, sitting blood pressure) were measured at Screening, before Baseline and the second day of Baseline, before Doses 1 and 7, and before checkouts (either Day 8 or 9 of each period).

f Hematology and serum chemistries. Laboratory tests were performed on specimens taken at the Screening Visit and on Day 8 of Period 2.

g Urine drug and alcohol screening were performed at Screening Visit and at check-ins for all overnight clinic visits.

h Pregnancy testing was performed at Screening and at overnight check-ins (Day 0 and Day 6) for each dosing segment for each trial period.

i At the Screening Visit, the nasogastric pH probe was inserted and the location of the upper border of the lower esophageal sphincter (LES) was made using manometry.

j Doses 1 and 7 in Periods 1 and 2 were administered in the trial clinic and subjects remained in clinic for the 24-hour postdose periods. Subjects took daily Doses 2 through 6, of each period in the morning in the clinic after an overnight fast and were observed for 1 hour (fasting, no water) and then released. Subjects were then allowed to consume food and drink per protocol.

k On Days 1 and 7, standardized meals were provided at 1, 5 and 10 hours postdose (ie, after test article or water for baseline).

l Blood samples (5 mL) were taken just prior to dosing, and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) after dosing on Days 1 and 7.

m Blood samples (5 mL) were taken just prior to the meal initiation, and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) after dosing.

n The pH probe was placed 10 cm below the upper border of the LES and the pH had to be <2.5. The inserted probe had to be tolerated by the subject for at least 15 minutes at the Screening Visit.

o For baseline evaluations, a volume of 120 mL of water was administered 1 hour after initiating pH monitoring. Continuous pH monitoring occurred from 1 hour prior to, through 24 hours after water administration.

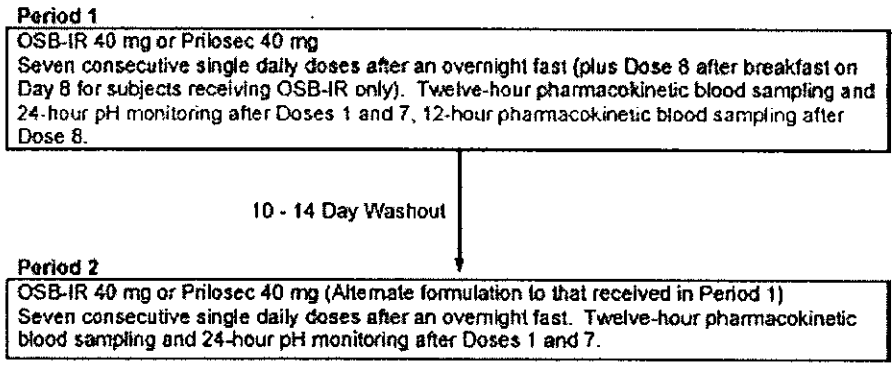
p For Days 1 and 7 dosing segments, continuous pH monitoring occurred from 1 hour before dosing through 24 hours after dosing.

The following laboratory tests were conducted on samples collected:

Blood Chemistry	Hematology	Urine
Albumin	Hematocrit	Amphetamines
Alkaline phosphatase	Hemoglobin	Benzodiazepines
β-HCG	CBC with differential	Cocaine

Blood urea nitrogen (BUN)	Platelet count	Ethanol
Creatinine		Opiates
Alanine aminotransferase (ALT)		Tetrahydrocannabinol
Aspartate transaminase (AST)		
Total bilirubin		
Total protein		

Figure 1: OSB-IR-C02 Trial Flow Diagram (Two-Way Randomized Crossover)



Adapted from sponsor's electronic submission TrialOSB-IR CO2 p.21

Treatments

A	OSB-IR 40 mg, overnight fast, 1 hour premeal	OSB-IR 40mg orally as a 20ml aqueous susp followed by 100ml each morning, 1 hr before breakfast
B	Prilosec 40mg overnight fast, 1 hour premeal	Prilosec 40mg orally with 120ml water each morning, 1 hr before breakfast
Dose 8	OSB-IR 40 mg, postmeal, 1 hr after meal start	OSB-IR 20mg orally as a 20ml aqueous susp, followed by 100ml water on Day 8 in Period 1hr after breakfast

The randomization of treatment sequences was generated by [ ] in Statistical Analysis System (SAS) using a consistent block size to provide a ratio of 1:1 for treatment sequences (AB:BA) and included randomizations for a total of 36 subjects. The random number generator used was the SAS function RANUNI.

Dose Selection

The 40 mg dose was studied in support of the OSB-IR 40 mg dose being developed for prevention of stress-related upper GI bleeding in critically ill patients and in order to

reference the Prilosec efficacy data supporting the indication for short-term treatment of active benign gastric ulcer.

Study Population

Up to 36 subjects were to be enrolled to ensure that at least 24 subjects completed all treatments with pharmacokinetic data after the seventh dose in Periods 1 and 2, and at least 20 subjects completed the trial with both pharmacokinetic and pharmacodynamic data for the seventh dose in Periods 1 and 2. Thirty-two subjects were dosed and 31 subjects completed the trial and 24 had both pharmacokinetic and pharmacodynamic data for Doses 1 and 7.

Inclusion Criteria

- Healthy non-Asian subjects, either male or non-lactating, non-pregnant females who were postmenopausal, sterile, or using an acceptable birth control method.
- 18 to 45 years of age, between 120 and 200 pounds and were within ± 20% of ideal body weight.
- Could tolerate installation of nasogastric pH probe at Screening and had a pH < 2.5.
- In good health on the basis of history, physical examination, and laboratory values.
- Had not used any form of tobacco (eg, smoking, chewing) for the last year.
- Could swallow a tablet or capsule without difficulty.
- Signed an approved informed consent form.

Exclusion Criteria

- Any significant history of/or concurrent gastrointestinal diseases or conditions, such as gastroesophageal reflux disease (GERD), heartburn, reflux esophagitis, peptic ulcer disease (gastric or duodenal), or a family history of peptic ulcer disease, gastric surgery (eg, vagotomy, pyloroplasty).
- Significant medical history or concurrent illness, such as respiratory, allergic, psychiatric, neurological, renal, hepatic, cardiovascular, metabolic or endocrine condition, or any other medical condition that the investigator or medical monitor considered sufficiently serious to interfere with the conduct, completion, or results of this trial or constituted an unacceptable risk to the subject.
- History of significant drug allergy or known hypersensitivity to any of the ingredients in the trial drugs.
- Positive urine test for alcohol or other drugs at any trial visit.
- Taking any gastric antisecretory drugs (eg, H2-receptor antagonists or PPIs, or antacids [including over-the-counter {OTC} medications]) within 14 days prior to Period 1 or during the trial.
- Had ingested grapefruit juice within 7 days of dose administration in any trial period.
- Had donated blood within 30 days of entering the trial.

- Had been treated with any investigational drug or therapy, or participated in a clinical trial in the 30 days prior to entering the trial.
- Any condition that could interfere with assessments, pose additional risks in administration of the trial drug to the subject, or preclude completion of the trial including a history of noncompliance, alcoholism, or drug abuse.
- Any laboratory test result deviating by more than 20% from the normal reference ranges of the local laboratory, if the investigator judged the abnormality to be of possible clinical significance.
- Evidence of infection with human immunodeficiency virus (HIV) (to protect safety of research staff).
- A known carrier of hepatitis B surface antigen or hepatitis C antibody.

Concomitant Therapy

Subjects were not allowed to use any prescription or OTC medications (except birth control) throughout this trial. Any use of concomitant medications could have resulted in the subject's termination from this trial. In the event a subject used a concomitant medication, the investigator was to contact the Santarus, Inc. monitor to discuss whether the particular subject should be discontinued. All concomitant medications were recorded in the CRF.

Withdrawal of Subjects

A subject could be withdrawn from the trial at any time at either the investigator's discretion or the subject's request. The primary reason for discontinuing participation in the trial was to be stated in the Case Report Form (CRF) and included, but was not limited to, one of the following:

- Presence of any abnormal clinical laboratory results resulting in the investigator's decision that allowing the subject to continue in the trial would be ill-advised.
- Use of unapproved concomitant medications.
- Occurrence of intolerable AEs.
- Withdrawal of consent by subject ("personal").
- Noncompliance with protocol (e.g., the subject failed to appear at one or more visits in spite of being encouraged to come).
- Development of an intercurrent illness, injury, or medical condition likely to interfere with subject safety, the overall assessment, or the required administration of trial medication.
- Development of any condition for which the investigator felt treatment withdrawal was justified.
- Termination of the trial by the sponsor.

If a subject was discontinued from the trial, the following procedures were to be performed:

- A physical examination and record vital signs and body weight
- Blood test for clinical laboratory analysis (including pregnancy testing)
- Record any AEs or medications used since previous visit
- Complete End of Treatment Status CRF

Subjects who discontinued from the trial for AEs were to be treated and followed according to established medical practice.

Safety

A complete physical examination, vital sign measurements, and clinical laboratory assessments were performed (see table 1). A pregnancy test (serum β-HCG) was performed on samples taken from females at the Screening Visit and at each admission into the clinic site (i.e., Days 0 and 6 of each period). Results from pregnancy testing and urine alcohol and drug screens were reviewed before the next dose of trial drug was administered.

Adverse Events

The intensity, duration, and relationship to treatment of AEs and the use of concomitant medications were evaluated. Changes from baseline in physical examination findings, vital sign measurements, and clinical laboratory test results were evaluated. All adverse events were recorded on the CRF during the trial even if the AE was assessed by the investigator as unlikely to be causally related to trial drug treatment.

The investigator was required to notify Santarus of any SAE by SAE Fax Form if an event occurred within 30 days after a subject had completed treatment in this clinical trial and if such event was judged to be probably or possibly related to test article.

Details of any AEs that occurred were collected during each trial period. After the subject had an opportunity to spontaneously mention any problems, the investigator or assigned staff inquired about AEs by asking the following standard questions:
At clinic check-ins:
1. "Have you had any medical problems since your last visit?"
2. "Have any medical problems present at your last visit changed, i.e., stopped, worsened, or improved?"
3. "Have you taken any medicines, other than trial drug, since your last visit?"

Efficacy

There were no efficacy measurements in this trial.

Endpoints

Pharmacokinetic Endpoints:

Primary
The primary endpoint was AUC(0-inf) for the ratio of OSB-IR to Prilosec for the seventh dose of each omeprazole formulation was evaluated using standard bioequivalence criteria.

Secondary
- AUC(0-inf) for the first dose of each omeprazole formulation
- Cmax after the first and seventh dose of each omeprazole formulation
- Time at which Cmax is observed (Tmax), elimination rate constant (kel), half-life of drug elimination (T½), and area under the plasma drug concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)] after the first and seventh doses of each omeprazole formulation
- Pharmacokinetic parameters obtained with OSB-IR administered postmeal

Pharmacodynamic Endpoints:

- Percent decrease from baseline in *integrated gastric acidity* for the 24-hour interval after the seventh dose of each omeprazole formulation
- Percent decrease from baseline in *mean gastric acid* concentration and in the percent time gastric pH was ≤ 4, and the increase from baseline in median gastric pH for the 24-hour interval after the seventh dose of each omeprazole formulation
- Percent decrease from *baseline in integrated gastric acidity*, mean gastric acid concentration, and the percent time gastric pH was ≤ 4, and the increase from baseline in median gastric pH for the 24-hour interval after the first dose of each omeprazole formulation

Pharmacokinetic Sampling, Analytical Methods, and Parameters

Blood samples (5 mL) were to be taken within 30 minutes before the dose and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) after the dose on Days 1 and 7 of both periods and Day 8 of Period 1. Zero time was the time that the subject swallowed a capsule or the first 20 mL of liquid formulation of trial drug.

Plasma omeprazole concentrations were measured using a previously validated liquid chromatography mass spectrometry (LC-MS/MS) assay. The assay range was 5.0 to 750 ng/mL.

The following pharmacokinetic parameters were evaluated:
- Plasma omeprazole concentration at each sampling time
- Cmax and the time at which Cmax is observed (Tmax) obtained directly from the data

without interpolation

- Elimination rate constant (kel) determined from a log-linear regression analysis of the terminal plasma omeprazole concentrations
- Half-life of drug elimination (T½) calculated as ln2/kel (using kel calculated for each respective period and dose)
- Area under the plasma drug concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)] calculated using the trapezoidal rule with the plasma concentration at time "t" being the last measurable concentration
- AUC(0-inf) calculated as AUC(0-t) + Ct/kel, where Ct is the last measurable plasma concentration (using kel calculated for each respective period and dose)

Gastric pH levels were measured at screening and on Days 0 (baseline), 1, and 7 of each period. At screening, gastric pH levels were measured to establish subjects' eligibility for enrollment.

Pharmacodynamic Parameters and Methodology

The following pharmacodynamic parameters were evaluated for each 24-hour period in 15-minute intervals:

- Integrated gastric acidity, calculated as follows:
  - Acid concentration (mM) = 1000 x 10-pH
  - Acidity (mmol* hr/L)= (acid in mM at time "t"+ acid in mM at time "t-1")/2 x (t – t-1)
  - Integrated gastric acidity expressed as mM x time, ie, mmol* hr/L
- Mean gastric acid concentration: calculated as 4 x integrated acidity for the 15-minute interval
- Median gastric pH
- Percent time gastric pH ≤ 4

Statistical Methods

Safety parameters were summarized by treatment using descriptive statistics and include all subjects who received one or more doses of trial drug.

Pharmacokinetics:

Pharmacokinetic parameters were evaluated using standard criteria for bioequivalence. A parametric (normal-theory) general linear model was applied to the logarithmic transformations of the area under the plasma drug concentration curve (AUC) and Cmax values. The 90% confidence intervals (90% CIs) for treatment differences (OSB-IR vs Prilosec) were calculated for log-transformed AUC and Cmax. These confidence intervals were then reverse transformed and multiplied by 100 to represent confidence intervals about the treatment mean ratios on a percentage scale. Analysis of variance (ANOVA) was also applied to the same parameters to evaluate differences in the

pharmacokinetics of omeprazole when OSB-IR 40 mg was given before and after a meal. The 90% CIs for the treatment mean ratios (postmeal:premeal) were calculated.

Pharmacodynamics:

Pharmacodynamic parameters were evaluated using standard criteria for bioequivalence. The baseline values for integrated gastric acidity were compared between the two treatment periods using an ANOVA model. If there were no statistically significant differences between the baselines, an ANOVA model was applied to the values of log-transformed integrated gastric acidity without any adjustment for baseline. The 90% CI was calculated for the ratio of treatment means (OSB-IR versus Prilosec) on the log-transformed scale. These confidence limits were then reverse transformed back to the original scale of measurement to represent confidence intervals about the treatment mean ratios on a percentage scale.

Ethics

This research was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the US 21 CFR Part 312.20 and the principles enunciated in the latest version of the Declaration of Helsinki.

Results

Patient Characteristics

Table 2 : Demographic Summary for All Subjects

Trait		Female	Male	Overall
Gender	Female	14	0	14
	Male	0	18	18
Race	Caucasian	5	5	10
	Hispanic	9	13	22
Frame Size	Small	1	7	8
	Medium	9	9	18
	Large	4	2	6
Age (years)	Mean	32	31	31
	SD	7	7	7
	Min	22	19	19
	Max	42	44	44
	N	14	18	32
Weight (pounds)	Mean	145.0	173.9	161.3
	SD	15.7	18.3	22 3
	Min	126.0	140.0	126.0
	Max	190.0	200.0	200 0
	N	14.0	18.0	32.0
Height (inches)	Mean	64.4	68.5	66.7
	SD	2.1	2.1	2 9
	Min	61.5	65.0	61.5
	Max	68.0	72.0	72.0
	N	14.0	18.0	32.0

Adapted from sponsor's electronic submission TrialOSB-IR CO2 p.40

Medical Officer Comments: There were 18 (56%) males and 14 (44%) females in the trial. Approximately 69% were Hispanics and 31% were Caucasians. The mean age was 31 years with a range from 19-44 years. It was noted that there were no clinically significant differences in the demographic or baseline characteristics (medical histories, physical findings, vital signs) between the females and males participating in this trial.

Patient Accounting

A total of 34 subjects entered the trial; 32 received at least one dose of trial drug, and 31 subjects completed the trial. Two subjects (Subjects 31 and 32) were withdrawn from the trial, because of abnormal laboratory results at screening, before receiving any trial drug. One subject (Subject 3) discontinued OSB-IR after the sixth dose in Period 2 because of an adverse event, otitis media.

Subject 6 missed the third dose of Prilosec because she did not return to the clinic; this subject was included in the Day 7 Prilosec dataset. Subject 1 had measurable omeprazole concentrations after the first dose of Prilosec, but not after the seventh dose of Prilosec; it is possible that this subject did not ingest this dose of Prilosec.

Pharmacokinetic Results

Table 3: Summary of Day 1 (Premeal) Plasma Omeprazole Pharmacokinetic Parameters for OSB-IR 40 mg and Prilosec 40 mg

	Plasma Omeprazole							
	OSB-IR 40 mg			Prilosec 40 mg				
Parameters*	N**	Arithmetic Mean	SD	N**†	Arithmetic Mean	SD	% Mean Ratio‡	90% CI for % Mean Ratio
Cmax (ng/mL)	32	1412	616.2	32	1040	579.1	-	-
Tmax (hr)	32	0.44	0.19	32	2.34	2.40	-	-
AUC(0-t) (ng*hr/mL)	32	2180	2254	32	2460	2546	-	-
AUC(0-inf) (ng*hr/mL)	32	2228	2379	31	2658	2888	-	-
T½ (hr)	32	1.00	0.63	31	1.21	0.73	-	-
kel(1/hr)	32	0.89	0.38	31	0.73	0.30	-	-
ln(Cmax)	32	7.15	0.47	32	6.74	0.74	151.10	124.02-184.09
ln[AUC(0-t)]	32	7.34	0.80	32	7.41	0.91	93.21	83.92-103.53
ln[AUC(0-inf)]	32	7.35	0.80	31	7.49	0.87	87.87	82.39-93.71

Adapted from sponsor's electronic submission TrialOSB-IR CO2 p.41

* Values for Cmax, AUC(0-t), and AUC(0-inf) are rounded to four significant figures and all other parameters are rounded to two decimal points after statistical analyses are performed.

** Subjects 1 and 3 are included in this table, although the statistical analysis plan indicated that only subjects completing both 7-day treatment periods would be included.
† Subject 7 is not included in the analyses of AUC(0-inf), T½, kel, and ln[AUC(0-inf)] because the kel could not be calculated since there was no clear log-linear decline in plasma omeprazole concentrations.
‡ % Mean Ratio = 100 * exp(OSB-IR - Prilosec); based on least-squares means.

Medical Officer Comments: The above table shows that after one dose, OSB-IR 40 mg and Prilosec 40 mg were bioequivalent with respect to AUC but not to Cmax. The least-squares mean ratio for OSB-IR to Prilosec was 87.9% for AUC(0-inf) with the boundaries of the 90% CI within 80% and 125% compared with Prilosec. The Cmax for OSB-IR 40 mg was higher than for Prilosec 40 mg (mean ratio 151.10%, 90% CI of 124.02% to 184.09%). The Tmax value for OSB-IR was shorter (0.44 hr) than the Tmax value for Prilosec (2.34 hr) (p < 0.001).

Table 4: Summary of Day 7 (Premeal) Plasma Omeprazole Pharmacokinetic Parameters for OSB-IR 40 mg and Prilosec 40 mg

	Plasma Omeprazole							
	OSB-IR 40 mg			Prilosec 40 mg				
Parameters*	N**	Arithmetic Mean	SD	N†	Arithmetic Mean	SD	% Mean Ratio ‡	90% CI for % Mean Ratio
Cmax(ng/mL)	31	1954	654.0	31	1677	645.5		-
Tmax(hr)	31	0.58	0.22	31	1.77	0.90		-
AUC(0-t) (ng*hr/mL)	31	4555	2586	31	4506	2522		-
AUC(0-inf) (ng*hr/mL)	31	4640	2741	31	4591	2639		-
ln(Cmax)	31	7.51	0.40	31	7.34	0.43	119.50	107.23 - 133.17
ln[AUC(0-t)]	31	8.26	0.62	31	8.25	0.62	101.99	95.37 - 109.06
ln[AUC(0-inf)]	**31**	**8.27**	**0.63**	**31**	**8.26**	**0.63**	**101.91**	**95.25 – 109.02**

Adapted from sponsor's electronic submission Trial OSB-IR ICO2 p.42

* Values for Cmax, AUC(0-t), and AUC(0-inf) are rounded to four significant figures and all other parameters are rounded to two decimal points after statistical analyses are performed.
** Subject 1 had omeprazole concentrations below the limit of quantification after Dose 7 of Prilosec and is not included in the summary statistics for Prilosec; however, was included in the summary statistics for OSB-IR.
† Subject 3 discontinued the trial before Dose 7 of OSB-IR and is not included in the summary statistics for OSB IR; however, this subject is included in the summary statistics for Prilosec.
‡ % Mean Ratio = 100 * exp(OSB-IR - Prilosec); based on least-squares means.
Note: Primary pharmacokinetic endpoint was ln[AUC(0-inf)] on Day 7.

Medical Officer Comments: The above table shows that at steady state (Day 7), OSB-IR 40 mg and Prilosec 40 mg administered once a day in the morning were bioequivalent; the least-squares means ratio was 101.91% with a 90% CI of 95.25% to 109.02%. The Cmax for OSB-IR 40 mg at steady state was slightly higher than for Prilosec (mean ratio of 119.50%, 90% CI of 107.23% to 133.17 %). The Tmax value for the immediate-release product was shorter (0.58 hr) than the Tmax value for Prilosec (1.77 hr) (p < 0.001).

Table 5: Summary of OSB-IR 40 mg Postmeal (Day 8) vs OSB-IR 40 mg Premeal (Day 7) Plasma Omeprazole Parameters at Steady State

	Plasma Omeprazole							
	OSB-IR 40 mg (Postmeal)			OSB-IR 40 mg (Premeal)				
Parameters*	N**	Arithmetic Mean	SD	N**	Arithmetic Mean	SD	% Mean Ratio ‡	90% CI for % Mean Ratio
Cmax (ng/mL)	16	880.6	378.7	16	2113	695 4	-	-
Tmax (hr)	16	1.47	0 71	16	0.55	0.20	-	-
AUC(0-t) (ng*hr/mL)	16	3778	2700	16	4838	2644	-	-
AUC(0-inf) (ng*hr/mL)	16	3862	2874	16	4941	2849	-	-
ln(Cmax)	16	6 68	0 52	16	7 59	0 43	40 25	34.87 - 46 46
ln[AUC(0-t)]	16	8.02	0.70	16	8.33	0.61	72.86	67.53 - 78.60
ln[AUC(0-inf)]	16	8.03	0.71	16	8.35	0.62	72.82	67.56 - 78.49

Adapted from sponsor's electronic submission Trial OSB-IR ICO2 p43

* Values for Cmax, AUC(0-t), and AUC(0-inf) are rounded to four significant figures and all other parameters are rounded to two decimal points after statistical analyses are performed.
** All subjects who received Dose 8 of OSB-IR 40 mg after a meal in Period 1 are included in the analysis.
‡ % Mean Ratio = 100 * exp(postmeal - premeal); based on least-squares means.

MOC: Ingestion of OSB-IR 40 mg 1 hour after taking a high-fat meal reduced the bioavailability to 72.82% [percent mean ratio (postmeal:premeal) for AUC(0-inf)] of the premeal value. Administration after the meal lowered the Cmax mean ratio (postmeal:premeal) to 40.25% and delayed the mean Tmax by 0.92 hours (55 minutes).

Pharmacodynamic Results

Results for integrated gastric acidity, mean gastric acid concentration, median gastric pH, and the percent time gastric pH was ≤ 4 are reported below.

Subjects 1, 2, 3, 5, 20, 30, 33, and 34 did not qualify for pharmacodynamic analyses because they did not have all six 24-hour pH records (ie, Baseline and Days 1 and 7 for each of the two periods).

Table 6: Cumulative Integrated Gastric Acidity (mmol* hr/L) with OSB-IR 40 mg and Prilosec 40 mg

	Integrated Gastric Acidity (mmol*hr/L)		OSB-IR / Prilosec (%)
Assessment	OSB-IR 40 mg	Prilosec 40 mg	By-Subject Ratios
Baseline	2194 (1421 - 2943)	2061 (1358 - 2762)	-
Day 1	556 (202 - 1217)	537 (169 - 1261)	-
Day 7	319 (26 - 512)	144 (21 - 557)	-
Percent Decrease from Baseline* to			
Day 1	70 (51 - 88)	76 (46 - 90)	97 (83 - 104)
Day 7	**84 (74 - 99)**	**93 (74 - 98)**	**100 (91 - 105)**

Adapted from sponsor's electronic submission Trial OSB-IR ICO2 p.49

* When calculating the percent decrease from Baseline, Baseline is the mean of the two baseline measurements. The percent decrease in integrated gastric acidity from Baseline to Day 1 (or Day 7) is calculated for each subject as follows: 100 x (Baseline - Day 1 (or Day 7)) / Baseline. OSB-IR / Prilosec (%) is calculated as the percent change from Baseline for OSB-IR divided by the percent change from Baseline for Prilosec. Table entries present the medians and boundaries of the interquartile range (25th and 75th percentiles) for integrated gastric acidity by trial day, the percent change from Baseline for OSB-IR and Prilosec, and the by-subject OSB-IR / Prilosec (%).

On Day 1, OSB-IR decreased integrated gastric acidity by 70% and and Prilosec by 76% (median). On Day 7, the corresponding median decreases were 84% (OSB-IR) and 93% (Prilosec). The median of the by-subject ratios (OSB-IR/Prilosec) of the decrease from baseline of integrated gastric acidity was 100%. As illustrated by the wide boundaries of interquartile ranges both at baseline and after treatment with both OSB-IR and Prilosec, there was substantial intersubject variation in the integrated gastric acidity. This magnitude of variation is typical for integrated gastric acidity before and after treatment.

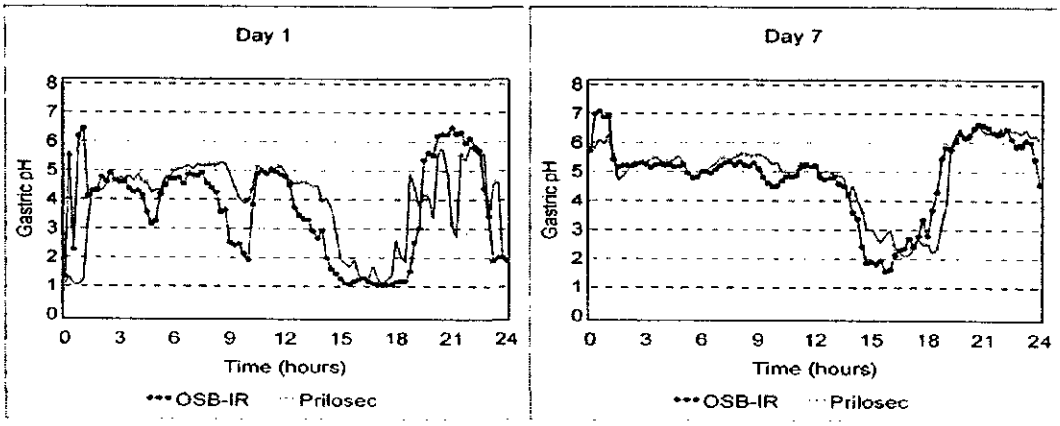
Table 7: Mean Gastric Acid Concentration (mM) with OSB-IR 40 mg and Prilosec 40 mg

	Mean Gastric Acid Concentration (mM)	
Assessment	OSB-IR 40 mg	Prilosec 40 mg
Baseline	91 (59 - 123)	86 (57 - 115)
Day 1	23 (8 - 51)	22 (7 - 53)
Day 7	13 (1 - 21)	6 (1 - 23)

Adapted from sponsor's electronic submission Trial OSB-IR ICO20 p52.

Note: The mean gastric acid concentration for the 24-hour recording period is obtained by dividing the 24-hour cumulative integrated gastric acidity for each subject by 24. Table entries present the medians and the boundaries of the interquartile range (25th and 75th percentiles) for these values by trial day.

Figure 8: Median Gastric pH with OSB-IR 40 mg and Prilosec 40 mg on Days 1 and 7



Adapted from sponsor's electronic submission Trial OSB-IR ICO20 p.55

Note: Each time point represents a 15-minute interval. Zero (0) time is the 15-minute interval just prior to the time of dosing. Values are displayed as medians for each 15-minute interval over the 24-hour recording period. Results are from 24 subjects.

This figure shows that on Day 1, there was an increase in median gastric pH during the first hour after dosing with OSB-IR (but not for Prilosec) likely due to the neutralization of gastric acid by the sodium bicarbonate in OSB-IR. Also, on Day 1 there was a greater decrease in gastric pH during each of three postprandial periods with OSB-IR than with Prilosec. On Day 7, the time-course for median gastric pH with OSB-IR was the same as that with Prilosec. There was no decrease in gastric pH below 4 for any of the three postprandial periods for either OSB-IR or Prilosec.

Table 9: Percent Time Gastric pH ≤ 4 with OSB-IR 40 mg and Prilosec 40 mg

	Percent Time Gastric pH ≤ 4	
Assessment	OSB-IR 40 mg	Prilosec 40 mg
Baseline	87	88
	(80 - 92)	(75 - 92)
Day 1	53	43
	(21 - 76)	(19 - 61)
Day 7	23	23
	(11 - 46)	(15 - 43)

Adapted from sponsor's electronic submission Trial OSB-IR ICO2 p.56

Note: The percent time gastric pH ≤ 4 is calculated for each 24-hour recording period for each of the 24 subjects. Table entries present the medians and the boundaries of the interquartile range (25th and 75th percentiles) of these values by trial day.

In this table, the median percent time gastric pH was ≤ was somewhat higher on Day 1 for OSB-IR (53) than for Prilosec (43), but were the same on Day 7. As shown in this table, there was considerable intersubject variability for both products on

Days 1 and 7. However, time plots for percent time gastric pH was <4 for individual subjects at Day 7, show remarkable intrasubject similarity between treatments.

Discussion

Clinical trial OSB-IR-C02 is a comparison of the pharmacokinetics and pharmacodynamics of 40 mg omeprazole sodium bicarbonate-immediate release (OSB-IR) suspension and Prilosec® delayed-release capsules in healthy subjects. A total of 34 subjects entered the trial; 32 received at least one dose of trial drug, and 31 subjects completed the trial. There were 18 (56%) males and 14 (44%) females in the trial.

Approximately 69% of the subjects were Hispanics and 31% were Caucasians. The mean age was 31 years with a range from 19-44 years. It was noted that there were no clinically significant differences in the demographic or baseline characteristics (medical histories, physical findings, vital signs) between the females and males participating in this trial.

Pharmacokinetic results shows that after one dose(day 1), OSB-IR 40 mg and Prilosec 40 mg were bioequivalent with respect to AUC but not to Cmax. The least-squares mean ratio for OSB-IR to Prilosec was 87.9% for AUC(0-inf) with the boundaries of the 90% CI within 80% and 125% compared with Prilosec. The Cmax for OSB-IR 40 mg was higher than for Prilosec 40 mg (mean ratio 151.10%, 90% CI of 124.02% to 184.09%). The Tmax value for OSB-IR was shorter (0.44 hr) than the Tmax value for Prilosec (2.34 hr) ($p < 0.001$).

On day 7 (at steady state), OSB-IR 40 mg and Prilosec 40 mg administered once a day in the morning were bioequivalent; the least-squares means ratio was 101.91% with a 90% CI of 95.25% to 109.02%. The Cmax for OSB-IR 40 mg at steady state was slightly higher than for Prilosec (mean ratio of 119.50%, 90% CI of 107.23% to 133.17 %). The Tmax value for the immediate-release product was shorter (0.58 hr) than the Tmax value for Prilosec (1.77 hr) ($p < 0.001$).

Ingestion of OSB-IR 40 mg 1 hour after taking a high-fat meal reduced the bioavailability to 72.82% [percent mean ratio (postmeal:premeal) for AUC(0-inf)] of the premeal value. Administration after the meal lowered the Cmax mean ratio (postmeal:premeal) to 40.25% and delayed the mean Tmax by 0.92 hours (55 minutes).

On Day 1, OSB-IR decreased integrated gastric acidity by 70% and and Prilosec by 76% (median). On Day 7, the corresponding median decreases were 84% (OSB-IR) and 93% (Prilosec). The median of the by-subject ratios (OSB-IR/Prilosec) of the decrease from baseline of integrated gastric acidity was 100%. As illustrated by the wide boundaries of interquartile ranges both at baseline and after treatment with both OSB-IR and Prilosec, there was substantial intersubject variation in the

integrated gastric acidity. This magnitude of variation is typical for integrated gastric acidity before and after treatment.

On Day 1, there was an increase in median gastric pH during the first hour after dosing with OSB-IR (but not for Prilosec) likely due to the neutralization of gastric acid by the sodium bicarbonate in OSB-IR. Also, on Day 1 there was a greater decrease in gastric pH during each of three postprandial periods with OSB-IR than with Prilosec. On Day 7, the time-course for median gastric pH with OSB-IR was the same as that with Prilosec. There was no decrease in gastric pH below 4 for any of the three postprandial periods for either OSB-IR or Prilosec.

The median percent time gastric pH was ≤ was somewhat higher on Day 1 for OSB-IR (53%) than for Prilosec (43%), but were the same on Day 7. As shown in this table, there was considerable intersubject variability for both products on Days 1 and 7. However, time plots for percent time gastric pH was <4 for individual subjects at Day 7, show remarkable intrasubject similarity between treatments.

In summary, in this study, the omeprazole used was an immediate release formulation (OSB-IR) compared to a delayed release (Prilosec) formulation. It was therefore anticipated that OSB-IR will have a Tmax that would occur earlier and a Cmax that would be higher than for Prilosec. The sponsor expected that the two products would be bioequivalent with regard to AUC and therefore also with regard to their pharmacodynamic effects.

OSB-IR and Prilosec were bioequivalent with respect to the primary endpoints: pharmacokinetic (AUC[0-inf]) and pharmacodynamic (percent decrease from baseline in 24-hour integrated gastric acidity) on Day 7 when using standard definitions of bioequivalence (mean ratios of test to reference and 90% CIs of 80% to 125%). However, they were not bioequivalent with regard to Cmax on either Day 1 or Day 7 with the upper boundary of the 90% confidence interval exceeding 125% on both days. The higher Cmax for OSB-IR was attributed to the elimination the delayed-release coating.

The presence of food reduced the omeprazole bioavailability of OSB-IR at steady state and reduced the rate of omeprazole absorption. Least-squares means Cmax and AUC(0-inf) were 40% and 73% of the Cmax and AUC(0-inf) for OSB-IR administered premeal, respectively. Mean Tmax was delayed by 55 minutes (p <0.001) when OSB-IR was administered postmeal.

Safety

Subjects who received at least one dose of either of trial drug were included in the safety analysis. Sixteen subjects (50%) received eight consecutive daily doses of OSB-IR 40 mg and 15 subjects (47%) received seven doses of OSB-IR 40 mg. A total of 31 subjects (97%) received seven consecutive doses of Prilosec 40 mg. One subject

(subject #3) discontinued from the trial because of an adverse event received seven doses of Prilosec and only six doses of OSB-IR.

Table 10: Number (%) of Subjects with Adverse Events (AE) by Treatment Group

MedDRA Body System Preferred Term	OSB-IR 40 mg n = 32 N (%)	Prilosec 40 mg n = 32 N (%)	Total n = 32 N (%)
Number of subjects with at least one adverse event	8 (25)	6 (19)	10 (31)
Ear and labyrinth disorders			
Ear pain	1 (3)	0 (0)	1 (3)
Eye disorders			
Eye pruritus	1 (3)	0 (0)	1 (3)
Gastrointestinal disorders			
Abdominal pain upper	1 (3)	0 (0)	1 (3)
Constipation	0 (0)	1 (3)	1 (3)
Loose stools	1 (3)	0 (0)	1 (3)
Nausea	1 (3)	2 (6)	3 (9)
Throat irritation	1 (3)	1 (3)	1 (3)
Infections and infestations			
Otitis media NOS	1 (3)	0 (0)	1 (3)
Pharyngitis viral NOS	0 (0)	1 (3)	1 (3)
Injury, poisoning and procedural complications			
Joint sprain	0 (0)	1 (3)	1 (3)
Nervous system disorders			
Headache NOS	2 (6)	2 (6)	3 (9)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	1 (3)	0 (0)	1 (3)
Skin and subcutaneous tissue disorders			
Dry skin	2 (6)	0 (0)	2 (6)
Pruritus NOS	1 (3)	0 (0)	1 (3)
Skin nodule	1 (3)	0 (0)	1 (3)

Adapted from sponsor's electronic submission Trial OSB-IR ICO2 p.37

A total of 8 subjects (25%) in the OSB-IR 40 mg group and 10 (31%) in the Prilosec 40 mg group experienced at least one adverse event (AE). The intensity of AEs were mild and are commonly observed in trials involving healthy subjects. None of the AEs was determined to be clinically significant.

There were no vital sign measurements that were reported as AEs and measurements were similar between subjects receiving OSB-IR and Prilosec.

On physical examination, the following adverse events were reported: subject #3 had otitis media (discontinued), subject #12 had skin nodule and subject 15 had dry itchy skin. These were classified as not related to the drug treatment (OSB-IR). No other clinically significant changes from baseline in the physical examination findings during this trial were reported.

There was no laboratory abnormality reported as an AE or any shifts or trends in any laboratory parameters during the trial. There were several subjects with chemistry and hematology test results that were slightly above or below the established normal range which were considered by the investigator to be not clinically significant in the context of this trial except for:

- **Subject #30: At screening had an elevated bilirubin result (2.0 mg/dL), which returned to normal range two days later (1.0 mg/dL); however, it was slightly elevated at the end of the trial (1.9 mg/dL).**
- **Subject #18: at Screening Visit had a slightly decreased hemoglobin level (10.7 g/dL); at the end of the trial had a lower hemoglobin level (9.0 g/dL) and hematocrit (27.8%).**
- **Subject #19 had a slightly decreased hemoglobin level at the end of the trial (10.3 g/dL).**
- **Subjects #23 and #25 had slightly elevated eosinophil counts before and during the trial.**

Up to eight consecutive doses of OSB-IR were well tolerated by the subjects participating in this trial.

Death

There were no deaths, serious AEs, or other significant AEs during this trial.

APPENDIX B
(*Labeling Recommendations*)

The following are my recommendations for labeling changes:

1. In the "**PRECAUTIONS**" section, under subsection "**General**", add the following sentences:

   "TRADE NAME" contains 1680 mg (20 mEq) of sodium bicarbonate. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, and respiratory alkalosis. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

   Clinicians should be aware of the amount of sodium bicarbonate contained in this formulation so that proper precaution could be exercised with its administration. Clinicians should also be reminded of the contraindications and/or precautions with the administration of sodium bicarbonate. Further, this drug is expected to be administered long-term; therefore, clinicians should exercise caution when prescribing this drug to

patients who chronically take large amounts of milk or calcium supplement as this can cause milk-alkali syndrome.

2. In the "**PRECAUTIONS**" section, under subsection "**Drug Interactions**", add the following sentences:

   There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time.

   The above sentences are recent class labeling changes made for all proton-pump inhibitors. Incorporating these changes will make the label consistent with the label of the listed drug, Prilosec® Delayed Release capsule.

3. In the "**PRECAUTIONS**" section, under subsection "**Pregnancy**", add the following sentences:

   Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase. There are no adequate and well-controlled studies in pregnant women.

   The above additional statements is for clinicians and patients to note that this formulation contains sodium bicarbonate and sodium, and that caution should be exercised when administered to pregnant women.

4. In the "**PRECAUTIONS**" section, under subsection "**Nursing Mothers**", the following sentences should be *deleted*:

   The above sentences should be *replaced* with the following sentences:

The above changes will make the label consistent with the currently approved label of the listed drug, Prilosec® Delayed Release capsule.

5. In the "**PRECAUTIONS**" section, under subsection "**Pediatric Use**", the following sentence should be added:

   There are no adequate and well-controlled studies in pediatric patients with "TRADE NAME" [ ]

   There were no Pediatric studies conducted by the sponsor in this omeprazole formulation containing sodium bicarbonate.

6. In the "**ADVERSE REACTIONS**" section, the following sentence should be added:

   Additional adverse reactions that could be caused by sodium bicarbonate, include metabolic alkalosis, seizures, and tetany.

   This formulation contains sodium bicarbonate; therefore, additional adverse reactions that can be caused by taking sodium bicarbonate should be included in the label. Some adverse reactions caused by omeprazole and sodium bicarbonate overlap, these are already listed in the sponsor's proposed label.

7. In the "**OVERDOSAGE**" section, the following sentence should be added:

   In addition, a sodium bicarbonate overdose may cause hypocalcemia, hypokalemia, hypernatremia, and seizures.

   Since this omeprazole formulation contains sodium bicarbonate, when a patient overdoses with OSB-IR, an overdose with sodium bicarbonate is also possible. Therefore, in patients with OSB-IR overdose, the diagnostic evaluation should include both omeprazole and sodium bicarbonate overdose.

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

/s/

Lolita Lopez
5/11/04 02:17:19 PM
MEDICAL OFFICER

Ruyi He
5/11/04 06:01:59 PM
MEDICAL OFFICER
I concur with Dr. Lopez's comments and recommendations.