CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-456

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22456	Submission Date(s): January 28, 2009; June 9, 2009 b(4)
Brand Name	Zegerid [redacted]
Generic Name	Omeprazole/sodium bicarbonate/magnesium hydroxide
Reviewers	PeiFan Bai, Ph.D.,
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology Products
Sponsor	Santarus, Inc
Submission Type; Code	Original
Formulation; Strength(s)	Tablets 40 mg, 20mg
Indication	Duodenal ulcer, benign gastric ulcer, gastroesophageal reflux disease(GERD) , erosive esophagitis (EE), maintain healing of erosive esophagitis

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1 Executive Summary

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided the labeling comments are adequately addressed by the sponsor.

1.2 Regulatory Background

Background of this submission: This NDA was submitted under 505(b)(2) section of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50, provisions to seek approval of Zegerid 20 and 40 mg immediate release tablets which contain both sodium bicarbonate and magnesium hydroxide for protecting omeprazole from rapid degradation by gastric acid.

In the Jan-28-09 submission, the sponsor only submitted the 40-mg strength of Zegerid —— tablets (omeprazole/sodium bicarbonate/magnesium hydroxide). On June 9, 2009, to the original NDA 22-456 submission the sponsor submitted an amendment to seek approval of the 20-mg strength of Zegerid —— tablets. b(4)

The proposed indications for Zegerid —— tablets are the same as the approved indications for Zegerid with magnesium hydroxide chewable tablets (NDA 21-850). The bridging pharmacokinetic study submitted for the 40-mg formulation is study OME-IR(TAB)-C23),entitled " A single dose, randomized, crossover bioequivalence trial of omeprazole administered as Zegerid ——40 mg and Zegerid with magnesium hydroxide chewable tablets 40 mg in healthy subjects." However, there is no bridging pharmacokinetic study conducted for the 20-mg formulation of Zegerid —— as compared to Zegerid with magnesium hydroxide chewable tablets 20 mg. The Biopharm Team of ONDQA decided that there is no need for the sponsor to conduct a bioequivalence PK study for the 20-mg strength (June-12-09 e-mail). b(4) b(4)

The tablets are manufactured to contain either 20 mg or 40 mg omeprazole USP, in combination with 750 mg of sodium bicarbonate USP (9 mEq) and 343 mg of magnesium hydroxide (12 mEq). When taken orally, this formulation enables rapid absorption of omeprazole. According to the sponsor, sodium bicarbonate and magnesium hydroxide in the Zegerid —— tablet formulation protect the acid labile omeprazole from gastric acid degradation. This distinguishes Zegerid —— from delayed-release tablets or capsules, which use enteric coatings to protect the omeprazole." In the August-09 meeting between OTC and DGP, it was decided that sodium bicarbonate should be treated as an active ingredient. Since sodium bicarbonate is on the OTC monograph, there is no requirement for conducting a bioequivalence study for this component. There is no discussion about magnesium hydroxide, which is still treated as a —— ingredient. b(4) b(4)

The reference product for this submission: On May 25, 2005, Santarus submitted NDA 21-850 under 505(b)(2) section of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50, provisions to seek approval of Zegerid 20 and 40 mg immediate release (IR) chewable tablets which contain both sodium bicarbonate and magnesium hydroxide for protecting omeprazole from rapid degradation by gastric acid. NDA 21-850 was approved based on demonstration of AUC bioequivalence of Zegerid with magnesium hydroxide 20 and 40 mg IR chewable tablets to Prilosec delayed release (DR) 20 and 40 mg capsule, respectively.

A DSI written request dated April 13, 2009 was issued with regard to study OME-IR (TAB) -C23.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

An open-label, randomized, 2-period crossover trial was conducted to determine whether Zegerid ——— tablets 40 mg is bioequivalent to Zegerid with magnesium hydroxide chewable tablets 40 mg in 127 healthy subjects. In each period, subjects received a single dose of Zegerid ——— tablets or Zegerid chewable tablets, administered 1 hour prior to beginning a standardized high-fat breakfast after an overnight fast. One Zegerid ——— tablet 40 mg or one Zegerid chewable tablet 40 mg was administered with 120 ml of room temperature water as a single oral dose in the morning, 1 hour before breakfast on Day 1. The washout period was 7 days. The results are summarized below.

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Pharmacokinetic comparison between Zegerid Tablets 40 mg and Zegerid Chewable Tablets 40 mg

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	Zegerid ——— Tab	Zegerid Chewable Tab	% Mean ratio	90% CI
lnCmax	7.2 (0.55)	7.3 (0.54)	90.62	83.80-98.00
lnAUC(0-∞)	7.41 (0.73)	7.44 (0.74)	96.98	93.20-100.91
lnAUC(0-t)	7.41 (0.73)	7.44 (0.74)	96.98	93.19-100.94

Based on 505 (b)(2) provisions, the design of this pharmacokinetic bridging study is acceptable. The comparative pharmacokinetic results of omeprazole show that Zegerid ——— tablets 40 mg is bioequivalent to Zegerid with magnesium hydroxide chewable tablets 40 mg in 127 healthy subjects.

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According to the July-08-09 DSI report from C.T. Viswanathan (Associate Director, Bioequivalence, Division of Scientific Investigations), it is stated that **"Following the above inspections, DSI concludes that clinical and analytical data from OME-IR (TAB) - C23 are acceptable for the review."**

Bio-creep issue: From the efficacy perspective, since the current product has higher calculated exposure than Prilosec DR based on a cross-study comparison, it is expected that the current product would not be less effective. As compared to the current product, Zegerid suspension had a higher Cmax based on a cross-study comparison. Since the safety study of Zegerid suspension was reviewed and deemed satisfactory, the current product is considered acceptable from the safety point of view.
In summary, these cross-study comparisons suggest that bio-creep concerns could be dismissed.

The current submission has been reviewed and found acceptable from the clinical pharmacology perspective.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the proposed indications of Zegerid [redacted]? b(4)

The proposed indications are duodenal ulcer, benign gastric ulcer, gastroesophageal reflux disease(GERD) , erosive esophagitis (EE), maintain healing of erosive esophagitis

2.1.2 What are the proposed mechanisms of actions of Zegerid [redacted] b(4)

Omeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Omeprazole does not exhibit anticholinergic or H2 histamine antagonistic properties. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more. Omeprazole is acid labile and thus rapidly degraded by gastric acid. Zegerid [redacted]s an immediate-release tablet formulation that contains an antacid component (sodium bicarbonate magnesium hydroxide), which raises the gastric pH and thus protects omeprazole from acid degradation. b(4)

2.1.3 What are the proposed dosing regimens and route of administration?

The proposed route of administration for all the indications sought approval is oral. Zegerid [redacted]tablets should be taken on an empty stomach at least one hour before a meal. Zegerid [redacted]tablets should be swallowed with water. DO NOT USE OTHER LIQUIDS. b(4)

The following statements are from the sponsor. Because Zegerid [redacted]tablets contain magnesium hydroxide, the tablets should not be substituted for other dosage forms (e.g., ZEGERID Powder for Oral Suspension or ZEGERID Capsules). Since both the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg), two 20 mg tablets are not equivalent to one 40 mg tablet; therefore, two 20 mg tablets should not be substituted for one 40 mg tablet. b(4)

Table 1 The proposed dosing regimens for individual indications

Indications	Dosing regimens
Duodenal ulcer	20 mg once daily
Benign gastric ulcer	40 mg once daily for 4-8 weeks
Symptomatic GERD and no esophageal erosions	20 mg once daily for up to 4 weeks
Erosive esophagitis	20 mg once daily for 4-8 weeks
Maintenance of Healing of Erosive Esophagitis	20 mg once daily

2.1.4 What is the regulatory background?

Background of this submission: This NDA was submitted under 505(b)(2) section of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50, provisions to seek

approval of Zegerid 20 and 40 mg immediate release tablets which contain both sodium bicarbonate and magnesium hydroxide for protecting omeprazole from rapid degradation by gastric acid.

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In the Jan-28-09 submission, the sponsor only submitted the 40-mg strength of Zegerid ——tablets (omeprazole/sodium bicarbonate/magnesium hydroxide). On June 9, 2009, to the original NDA 22-456 submission the sponsor submitted an amendment to seek approval of the 20-mg strength of Zegerid —— tablets.

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The proposed indications for Zegerid —— tablets are the same as the approved indications for Zegerid with magnesium hydroxide chewable tablets (NDA 21-850). The bridging pharmacokinetic study submitted for the 40-mg formulation is study OME-IR(TAB)-C23),entitled " A single dose, randomized, crossover bioequivalence trial of omeprazole administered as Zegerid ——40 mg and Zegerid with magnesium hydroxide chewable tablets 40 mg in healthy subjects." However, there is no bridging pharmacokinetic study conducted for the 20-mg formulation of Zegerid —— as compared to Zegerid with magnesium hydroxide chewable tablets 20 mg. The Biopharm Team of ONDQA decided that there is no need for the sponsor to conduct a bioequivalence PK study for the 20-mg strength (June-12-09 e-mail).

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The tablets are manufactured to contain either 20 mg or 40 mg omeprazole USP, in combination with 750 mg of sodium bicarbonate USP (9 mEq) and 343 mg of magnesium hydroxide (12 mEq). When taken orally, this formulation enables rapid absorption of omeprazole. According to the sponsor, sodium bicarbonate and magnesium hydroxide in the Zegerid ——tablet formulation protect the acid labile omeprazole from gastric acid degradation. This distinguishes Zegerid —— from delayed-release tablets or capsules, which use enteric coatings to protect the omeprazole." In the August-09 meeting between OTC and DGP, it was decided that sodium bicarbonate should be treated as an active ingredient. Since sodium bicarbonate is on the OTC monograph, there is no requirement for conducting a bioequivalence study for this component. There is no discussion about magnesium hydroxide, which is still treated as a ——— ingredient.

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The reference product for this submission: On May 25, 2005, Santarus submitted NDA 21-850 under 505(b)(2) section of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50, provisions to seek approval of Zegerid 20 and 40 mg immediate release (IR) chewable tablets which contain both sodium bicarbonate and magnesium hydroxide for protecting omeprazole from rapid degradation by gastric acid. NDA 21-850 was approved based on demonstration of AUC bioequivalence of Zegerid with magnesium hydroxide 20 and 40 mg IR chewable tablets to Prilosec delayed release (DR) 20 and 40 mg capsule, respectively.

A DSI written request dated April 13, 2009 was issued with regard to study OME-IR (TAB) -C23.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies used to support dosing or label claims?

In supporting dosing and label claims, study OME-IR(TAB)-C23 is the key clinical pharmacology submitted to demonstrate that omeprazole administered as Zegerid ——— tablets 40 mg is bioequivalent to Zegerid with magnesium hydroxide chewable tablets 40 mg in healthy subjects. This study was an open-label, randomized. 2-period crossover trial. In each period, subjects received a single dose of Zegerid——— tablets or Zegerid chewable tablets, administered 1 hour prior to beginning a standardized high-fat breakfast after an overnight fast. One Zegerid——— tablet 40 mg or one Zegerid with Magnesium Hydroxide Chewable tablets 40 mg was administered with 120 ml of room temperature water as a single oral dose in the morning, 1 hour before breakfast on Day 1. The washout period was 7 days. Based on 505 (b)(2) provisions, the design of this pharmacokinetic bridging study is acceptable.

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2.2.2 Is Zegerid——— 40 mg bioequivalent to Zegerid with magnesium hydroxide chewable tablets 40 mg in healthy subjects with regards to omeprazole?

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The study was conducted in 134 healthy subjects (73 females and 61 males) with an average age of 26.7. The race and ethnicity breakdown shows that participants included 61 white Hispanic subjects, 47 white non-Hispanic subjects, and 21 African Americans, and 2 Hawaiian/Pacific Islanders. Only 127 subjects completed both treatment periods, three discontinued due to withdrawal of consent, and 4 discontinued due to noncompliance.

Table 2 The treatments administered are described below.

Treatment	Treatment Description
Zegerid tablets	Zegerid® with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablets 40 mg were swallowed followed by 120 mL (4 oz) of room temperature water, 1 hour before breakfast.
Zegerid chewable tablets	Zegerid® with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Chewable Tablets 40 mg were taken with 120 mL (4 oz) of room temperature water, 1 hour before breakfast.

During each period, Blood samples were taken 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes post dose. The plasma concentration time profiles of omeprazole are shown below.

Figure 1 Mean Plasma Omeprazole Concentrations after Administration of Zegerid ——— Tablets 40 mg and Zegerid Chewable Tablets 40 mg

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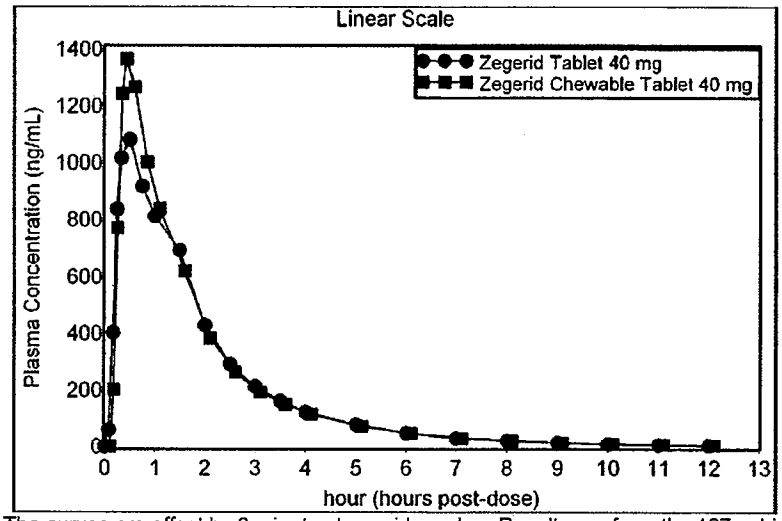

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The curves are offset by 6 minutes to avoid overlap. Results are from the 127 subjects who completed all trial periods. Zegerid Tablet has been renamed as Zegerid ——— Tablet.

The chewable tablet reached slightly higher Cmax and AUC than the tablet with sodium bicarbonate and magnesium hydroxide with Cmax being approximately 10% higher and AUC roughly 4%.

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Table 3 Arithmetic mean (CV%) of omeprazole pharmacokinetics following Zegerid ——— Tablets 40 mg or Zegerid Chewable Tablets 40 mg administered premeal.

	Zegerid ——— Tab	Zegerid Chewable Tab
Cmax(ng/ml)	1,528 (48.88%)	1,680 (48.29%)
$AUC_{(0-12)}$ (ng*hr/ml)	2,185 (86.06%)	2,275 (88.99%)
Tmax	0.68 (70.64%)	0.49 (74.62%)
T1/2	0.87 45.69%)	0.86 (50.78%)

N=127

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

The sponsor used AUC(0-∞) to demonstrate bioequivalence between the current product and chewable tablets. Based on the small difference between AUC(0-t) and AUC(0-∞), use of the latter for bioequivalence comparison is considered acceptable. Zegerid ——— Tablet 40 mg had a lower average omeprazole Cmax than Zegerid Chewable Tablet 40 mg, that is 1,528 (746.9) ng/ml vs 1680 (811.2) ng/ml. We recalculated the 90% confidence intervals and concluded that Zegerid ——— Tablet 40 mg is bioequivalent to Zegerid Chewable Tablet 40 mg.

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Table 4 Pharmacokinetic comparison between Zegerid ——— Tablets 40 mg and Zegerid Chewable Tablets 40 mg

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	Zegerid Tab	Zegerid Chewable Tab	% Mean ratio	90% CI*
lnCmax	7.2 (0.55)	7.3 (0.54)	90.62	83.80-98.00
lnAUC(0-∞)	7.41 (0.73)	7.44 (0.74)	96.98	93.20-100.91
lnAUC(0-t)	7.41 (0.73)	7.44 (0.74)	96.98	93.19-100.94

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N=127; Mean (SD); *calculated by reviewer.

Note: Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to four significant digits and all other parameters were rounded to two decimal places after statistical analyses were performed. Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.

2.2.3 What adverse events were observed during the bioequivalence study (Study OME-IR(TAB)-C23)?

Adverse events observed during Study OME-IR(TAB)-C23 are summarized below.

Table 5. Detailed adverse events observed during the study

MedDRA System Organ Class Preferred Term	Zegerid Tablets 40 mg (N=132) n	(%)	Zegerid Chewable Tablets 40 mg (N=130) n	(%)	Total (N=134) n	(%)
Overall	13	(9.8)	13	(10.0)	26	(19.4)
Psychiatric disorders	1	(0.8)	0	(0.0)	1	(0.7)
Anxiety	1	(0.8)	0	(0.0)	1	(0.7)
Nervous system disorders	4	(3.0)	8	(6.2)	12	(9.0)
Headache NOS	0	(0.0)	1	(0.8)	1	(0.7)
Paraesthesia	0	(0.0)	1	(0.8)	1	(0.7)
Vasovagal attack	4	(3.0)	6	(4.6)	10	(7.5)
Gastrointestinal disorders	6	(4.5)	4	(3.1)	10	(7.5)
Abdominal pain NOS	1	(0.8)	1	(0.8)	2	(1.5)
Abdominal pain lower	1	(0.8)	0	(0.0)	1	(0.7)
Nausea	4	(3.0)	3	(2.3)	7	(5.2)
Vomiting NOS	2	(1.5)	0	(0.0)	2	(1.5)
General disorders and administration site conditions	3	(2.3)	2	(1.5)	5	(3.7)
Rigors	1	(0.8)	0	(0.0)	1	(0.7)
Venipuncture site bruise	1	(0.8)	2	(1.5)	3	(2.2)
Venipuncture site pain	1	(0.8)	0	(0.0)	1	(0.7)

The number and percentage of subjects reporting at least one occurrence of an AE for each unique System Organ Class and Preferred Term are tabulated. At each level of summation (Overall, System Organ Class, Preferred Term), subjects were counted only once. The denominator for calculating percentages was the number of subjects who received at least one dose of the designated trial drug. Zegerid Tablets have been renamed as Zegerid Chewable Tablets.

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Overall, there were no clinically meaningful differences in the number or nature of AEs reported in this trial between the two trial products.

2.2.4 Are there any bio-creep concerns in terms of safety and efficacy since the current product is not compared head to head with Prilosec DR?

The reference product for this submission is Zegerid with Magnesium Hydroxide Chewable tablets 40 mg, which was approved based on a bioequivalence study with Prilosec delayed release (DR) 40mg. Naturally, there are concerns whether the current product may not be bioequivalent to Prilosec delayed release (DR) 40mg, and the efficacy and safety of omeprazole in the current product could be compromised.

Diagram of bioequivalence link:

1. Pharmacokinetic study only:
Zegerid ——— tablets 40 mg ——→ Zegerid with Magnesium Hydroxide Chewable 40 mg tablets ——→ Prilosec delayed release (DR) 40mg b(4)

2. A clinical safety study of Zegerid suspension plus
comparable pharmacokinetic study for Zegerid sodium bicarbonate suspension

Zegerid sodium bicarbonate suspension 40 mg——→ Prilosec delayed release (DR) 40mg

Table 6 Pair-wise comparisons of plasma omeprazole pharmacokinetic parameters between different Zegerid formulations.

		% Mean ratio	90% CI % Mean Ratio
Zegerid ——— Tab vs Zegerid Chewable Tab (single dose)	lnCmax	90.62	83.80-98.00
	lnAUC(0-∞)	96.98	93.20-100.91
Zegerid Chewable Tab vs Prilosec DR (steady state, 7 days)	lnCmax	129.96	118.83-142.12
	lnAUC(0-∞)	113.41	106.68-120.57
Zegerid sodium bicarbonate suspension vs Prilosec DR (steady state, 7 days)	lnCmax	119.50	107.23-133.17
	lnAUC(0-∞)	101.91	95.25-109.02

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The current product has lower Cmax and AUC than Zegerid Chewable tablets while Zegerid Chewable tablets have higher Cmax and AUC than Prilosec DR. Based on the calculation of the arithmetic mean ratios for Cmax and AUCt between the current product and Prilosec DR, the current product has slightly higher Cmax and AUCt (shown below). From the efficacy perspective, since the current product has higher calculated exposure that Prilosec DR, it is expected that the current product would not be less effective. Enclosed herein Zegerid suspension data are included as a reference for safety since there was a safety study conducted for the approved Zegerid suspension.

Zegerid suspension had slightly higher Cmax and AUC than Priolsec DR. Again, the calculated data were used to calculate the arithmetic mean ratio between the current product and Zegerid sodium bicarbonate suspension. Though this indirect comparison using the data from different studies is less than ideal, the calculated results show that the current product had slightly lower Cmax and slightly higher AUC than suspension. Since the safety study for Zegerid suspension was reviewed and deemed satisfactory, the current product with lower Cmax could be treated as acceptable from the safety point of view. In summary, these calculations along with the bioequivalence comparisons between these products, it is concluded that bio-creep concerns could be dismissed.

Table 7 Calculated arithmetic mean ratios between different pairs of Zegerid products based on cross-study comparisons

	parameter	Arithmetic mean ratio	comments
Zegerid [redacted] Tab (day 1) vs Prilosec DR (day 7)	Cmax	1.13	Calculations based results from two different BE studies (current submission and BE study between Chewable Tablet and Prilosec DR)
	AUC(0-t)	1.05	
Zegerid Sodium Bicarbonate Suspension vs Prilosec DR (steady state, 7 days)	Cmax	1.17	From the BE study comparing these two products
	AUC(0-t)	1.01	
Zegerid [redacted] (day 1) vs Zegerid sodium bicarbonate suspension (day 7)	Cmax	0.97	Calculations based on the above calculated results
	AUC(0-t)	1.04	

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2.3 General Biopharmaceutics

2.3.1 Is the to-be-marketed formulation identical to the one used for the bioequivalence trial?

The to-be-marketed formulation of 40 mg formulation is identical to the one used in bioequivalence trial 9 OME-IR(TAB)-C230.

2.3.2 What is the to-be-marketed formulation?

Table 8 Component and composition of the to-be-marketed formulation

Ingredient	Reference to Quality Standard	Manufacturer	Quantity (20 mg)	Quantity (40 mg)	Function
Omeprazole	USP				API
Sodium Bicarbonate	USP		750 mg	750 mg	API and
Magnesium Hydroxide	GRAS				API and
Hydroxypropyl Cellulose	NF				
Croscarmellose Sodium	NF				
Sodium Stearyl Fumarate	NF				
Total Weight/Unit					

** Magnesium hydroxide is equivalent to 343 mg of active magnesium hydroxide

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Each 20 mg and 40 mg Zegerid tablet contains 750 mg (9 mEq) of sodium bicarbonate (equivalent to 209 mg of Na+) and 343 mg (12 mEq) of magnesium hydroxide (equivalent to 143 mg of Mg2+).

Omeprazole protection against the acidic environment of the stomach required introduction of an antacid or an antacid combination capable of both rapidly raising the pH of the stomach to more neutral levels and maintaining this environment throughout the gastric transit time. Sodium bicarbonate is highly water soluble with an inherent pH close to neutral, and therefore optimal for ensuring sufficient omeprazole stability for effective bio-absorption. Magnesium hydroxide,

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The rationale and data supporting the use of sodium bicarbonate and magnesium hydroxide, as the preferred

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2.4 Analytical Section

2.4.1 What analytical methods were used to assess Omeprazole and its metabolites and were the analytical assay methods adequately validated?

Omeprazole in the plasma was quantified using Liquid Chromatography with Tandem Mass Spectrometry (LC-MS-MS). The assay method was validated for a range of 4.00 to 4000 ng/mL based on the analysis of 0.100 mL of human plasma.

Table 9 Back-calculated human EDTA omeprazole concentrations of calibration standards assayed in 45 separate batch runs are summarized below

Concentration [ng/mL]	A 4.00 ng/mL	B 8.00 ng/mL	C 40.0 ng/mL	D 100 ng/mL	E 500 ng/mL	F 2000 ng/mL	G 3600 ng/mL	H 4000 ng/mL
n	45	43	45	44	45	45	44	45
Overall Mean	4.01	7.89	40.7	104	493	1980	3530	3990
S.D.	0.106	0.429	1.61	4.18	22.0	63.8	124	152
%CV	2.6	5.4	4.0	4.0	4.5	3.2	3.5	3.8
%Bias	0.3	-1.4	1.8	4.0	-1.4	-1.0	-1.9	-0.3
Reason Deactivated								
* >15% Bias								

The quality control samples showed % bias of 6.7% for 12 ng/ml, 6.0 % for 1000 ng/ml. 3.0% for 2,000 ng/ml. and 3.4% for 3,200 ng/ml, and % precision of 93.9% for 12 ng/ml, 96.4 % for 1000 ng/ml, 94.1% for 2,000 ng/ml. and 95.6% for 3,200 ng/ml. Fifty standard curves each over the concentration range of 4 ng/ml to 4,000 ng/ml (4, 8, 40, 100, 500, 2,000, 3,600, and 4,000) showed correlation coefficients ranging from 0.9947 to 0.9998.

In short, the analytical method is acceptable and adequately validated.

3 Detailed Labeling Recommendations

The submitted Zegerid——labeling was reviewed and compared with those of Zegerid with magnesium hydroxide Chewable tablets and PRILOSEC (omeprazole) delayed-release capsules. The following recommendations are based on the newly approved labeling of PRILOSEC (omeprazole) delayed-release capsules. b(4)

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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4 Appendices

4.1 Individual Study Reviews

Please see appendix 4.2.1

4.2 OCP Filing/Review Form

Please see appendix 4.2.2

Appendix 4.2.1 Individual Study Review

1. Trial Number OME-IR(TAB)-C23

A Single Dose, Randomized, Crossover Bioequivalence Trial of Omeprazole Administered as Zegerid® with Magnesium Hydroxide Tablets 40 mg and Zegerid® with Magnesium Hydroxide Chewable Tablets 40 mg in Healthy Subjects

Name of Sponsor: Santarus, Inc.	Individual Trial Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid® with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablets 40 mg		
Name of Active Ingredient: Omeprazole		

Title of Trial: A Single Dose, Randomized, Crossover Bioequivalence Trial of Omeprazole Administered as Zegerid® with Magnesium Hydroxide Tablets 40 mg and Zegerid® with Magnesium Hydroxide Chewable Tablets 40 mg in Healthy Subjects	
Investigator: Jolene K. Berg, MD **Trial Center:** CEDRA Clinical Research LLC, San Antonio, Texas	
Publications: None at the time of this report.	
Date of First Subject Dosed: July 13, 2008 **Date of Last Subject Completed:** July 20, 2008	**Phase of Development:** 1
Objective: The objective of this trial was to demonstrate the equivalence of omeprazole administered as Zegerid with Magnesium Hydroxide Tablets 40 mg (Zegerid tablets) and Zegerid with Magnesium Hydroxide Chewable Tablets 40 mg (Zegerid chewable tablets) with respect to bioavailability (area under the curve [AUC(0-inf)]) on Day 1.	
Methodology: This was an open-label, randomized, 2-period crossover trial, with each subject receiving a single dose of Zegerid tablets and Zegerid chewable tablets. On Day 1 of Period 1, subjects received one of the two trial drugs (by randomization) 1 hour prior to a standardized high-fat breakfast after an overnight fast. A 7- to 10-day washout followed Period 1. On Day 1 of Period 2, subjects received the alternative trial drug to that received in Period 1. Blood samples were drawn just prior to dosing and over 12 hours postdose in each period for the determination of plasma omeprazole concentrations (see Pharmacokinetic Blood Sampling).	
Number of Subjects (planned and analyzed): With a type I (alpha) error of 0.05, a type II (beta) error of 0.10, a coefficient of variation for AUC(0-inf) of approximately 25% and with the test mean within 10% of the reference mean, a sample size of 120 evaluable subjects was considered sufficient to test pharmacokinetic (PK) bioequivalence using a randomized, 2-way crossover design. Assuming a 10% lost-to-follow-up rate, 134 subjects were planned and enrolled.	
Diagnosis and Main Criteria for Inclusion and Exclusion: Participants in this trial were non-Asian (male and nonlactating, nonpregnant female) healthy subjects who were between 18 and 45 years of age and who satisfied all inclusion and exclusion criteria.	
Trial Drug, Dose, Mode of Administration and Lot Number: One Zegerid® with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablet 40 mg (Lot 436428) was administered as a single oral dose in the morning, 1 hour before breakfast.	

Reference Product, Dose, Mode of Administration and Lot Number: One Zegerid® with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Chewable Tablet 40 mg (Lot 40115) was administered as a single oral dose in the morning, 1 hour before breakfast.

Duration of Participation: The duration of trial participation for each subject was approximately 5 weeks, including up to 21 days for Screening, and 7 to 10 days between Periods 1 and 2.

Criteria for Evaluation:

Efficacy: Efficacy was not evaluated in this trial.

Safety: Safety was assessed by evaluating laboratory test results, physical examination findings, vital signs and adverse events (AEs).

Pharmacokinetic Parameters: Omeprazole plasma concentrations were measured on Day 1 in each period. The following PK parameters were calculated:

- Plasma omeprazole concentration at each sampling time
- Peak plasma omeprazole concentration (Cmax) and time to peak plasma concentration (Tmax) obtained directly from the data without interpolation
- Terminal elimination rate constant (kel) determined from a log-linear regression analysis of the terminal plasma omeprazole concentrations
- Terminal elimination half-life (T½) calculated as 0.693/kel
- Area under the plasma omeprazole concentration-time curve from time zero to time "t" [AUC(0-t)] calculated using the trapezoidal rule with the plasma concentration at time "t" being the last measurable concentration
- Area under the plasma omeprazole concentration-time curve from time zero to time infinity [AUC(0-inf)] calculated as AUC(0-t) + Ct/kel, where Ct is the last measurable plasma concentration and kel is the terminal elimination rate constant defined above

Statistical Methods: The primary PK endpoint was the bioavailability of omeprazole [AUC(0-inf)] after a single dose of each omeprazole formulation.

An analysis of variance (ANOVA) model that included factors for treatment, period, sequence and subject nested within sequence was used to test the equivalence of Zegerid tablets and Zegerid chewable tablets using the natural logarithmic transformation of AUC(0-inf). A 90% confidence interval (CI) for treatment differences was calculated; the endpoints of this CI were then reverse transformed to represent a CI for the treatment mean ratios on the original scale. Equivalence was to be declared if the bounds of the 90% CI for the ratio of least-squares means for AUC(0-inf) of Zegerid tablets to Zegerid chewable tablets were within 80% to 125%.

Another PK endpoint was Cmax after a single dose of each omeprazole formulation. The ANOVA model was also used to test the equivalence of Zegerid tablets and chewable tablets using the natural logarithmic transformation of Cmax.

Summary of Results:

Safety Results: There were no deaths, serious adverse events (SAEs) or other AEs of clinical importance in this trial. Overall, there were no clinically meaningful differences in the number, nature, severity or duration of AEs reported in this trial between the two trial drugs. There were no clinically significant changes from Baseline (Screening) in physical examination findings or vital sign measurements.

Two patients were found to have elevation of liver function tests (bilirubin in subject 066, and ALT and AST in subject 123) from Baseline (Screening) to the Final Visit, which were possibly caused by Zegerid. No clinical signs or symptoms were associated with these abnormalities. Repeat testing within ten days after the Final Visit showed normal values for both patients. No other clinically significant changes in laboratory parameters were

observed in this trial.

Pharmacokinetic Results: A comparison of the PK parameters for Zegerid tablets and Zegerid chewable tablets administered premeal is presented in Table I.

Table I: Plasma Omeprazole Pharmacokinetic Parameters for Zegerid Tablets and Zegerid Chewable Tablets After a Single Dose Administered Premeal

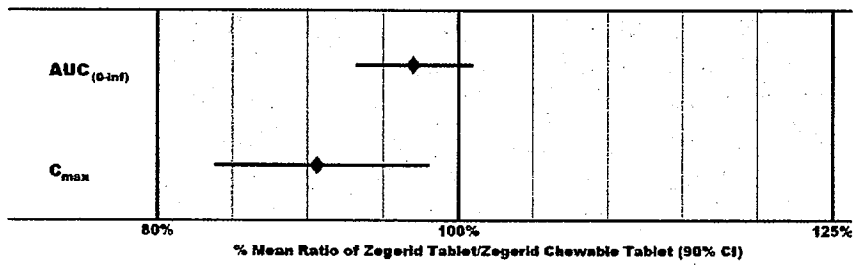
	Plasma Omeprazole							
	Zegerid Tablets 40 mg			Zegerid Chewable Tablets 40 mg				
Parameters*	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	127	1528	746.9	127	1680	811.2		
Tmax (hr)	127	0.68	0.48	127	0.49	0.37		
AUC(0-t) (ng*hr/mL)	127	2185	1881	127	2275	2025		
AUC(0-inf) (ng*hr/mL)	127	2203	1920	127	2298	2087		
T½ (hr)	127	0.87	0.40	127	0.86	0.44		
kel (1/hr)	127	0.93	0.33	127	0.96	0.37		
ln (Cmax)	127	7.20	0.55	127	7.30	0.54	90.62	83.80 - 98.00
ln [AUC(0-inf)]	127	7.41	0.73	127	7.44	0.74	96.98	93.20 - 100.91

Source: Post-text Tables 14.4-3, 14.4-4 and Appendix 16.1.9-2.
* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to four significant digits and all other parameters were rounded to two decimal places after statistical analyses were performed. Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.
Note: Subjects 021, 033, 058, 113, 114, 117 did not receive trial drug in Period 2 dosing. Subject 027 received trial drug in Period 2 but withdrew before completing blood sampling. These seven subjects were excluded from the pharmacokinetic analysis.

The bounds of the 90% CIs for the ratio of least-squares means for both AUC(0-inf) and Cmax were within the accepted regulatory of 80% to 125%. Thus, after a single dose, Zegerid tablets and Zegerid chewable tablets were bioequivalent.

Conclusion: After a single dose, Zegerid tablets and Zegerid chewable tablets are bioequivalent. A similar profile of mean plasma omeprazole concentrations was observed over the 12-hour sampling period for the two Zegerid formulations.

Figure I: Summary of Pharmacokinetic Bioequivalence for Zegerid Tablets and Zegerid Chewable Tablets



Source: Appendix 16.1.9-2.

2. Trial Number: OSB-IR-C02

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

Name of Sponsor: Santarus, Inc. **Name of Finished Product:** OSB-IR (Omeprazole Sodium Bicarbonate-Immediate Release) **Name of Active Ingredient:** Omeprazole	Individual Trial Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

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

Investigator: Mark J. Allison, MD
Trial Center: MDS Pharma Services, 4639 South 36th Street, Phoenix, AZ 85040

Publication (reference): None.

Date of First Subject Enrollment: May 10, 2002 **Date of Last Subject Completed:** July 8, 2002	**Phase of Development:** I

Trial Objectives:

Primary Pharmacokinetic Objective: The primary pharmacokinetic objective was 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 0 time and extrapolated to infinity [AUC(0-inf)] after the seventh consecutive daily dose of each omeprazole formulation.

Secondary Pharmacokinetic Objectives: The secondary pharmacokinetic objectives were as follows:

1. To assess whether OSB-IR is equivalent to Prilosec with regard to peak plasma concentration (Cmax) after the seventh dose of each omeprazole formulation
2. To test the hypothesis that OSB-IR is bioequivalent to Prilosec after the first dose of each omeprazole formulation
3. 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: The secondary pharmacodynamic objectives were as follows:

1. 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
2. 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
3. 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.

Methodology: This was 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 that had 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.

Safety assessments consisted of physical examination, vital sign measurements, clinical laboratory testing, monitoring for adverse events (AEs), and monitoring for use of concomitant medications.

Number of Subjects (planned and analyzed): 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.

Diagnosis and Main Criteria for Inclusion and Exclusion: Subjects were healthy, male or nonlactating, nonpregnant female subjects, 18 to 45 years of age, between 120 and 200 pounds, who satisfied all inclusion and exclusion criteria.

Test Product, Dose and Mode of Administration, Batch Number: OSB-IR 40 mg (Lot Number F1021C002) administered orally as a 20 mL aqueous suspension followed by 100 mL water once daily for seven or eight consecutive days.

Duration of Treatment: Subjects participated in this trial for up to 43 days. This included up to 14 days for screening, one 7- or 8-day treatment period, a 10- to 14-day washout period, and one 7-day treatment period.

Reference Product, Dose, Mode of Administration, and Batch Number: Prilosec® (omeprazole, manufactured for AstraZeneca by Merck & Co. Inc., Lot Number M1952), 40 mg delayed-release enteric-coated capsules, administered orally with 120 mL water once daily for seven consecutive days.

Criteria for Evaluation:

There were no efficacy measurements in this trial except for pharmacodynamic evaluations, which are discussed below.

Safety: 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.

Pharmacokinetic Endpoints:

Primary Endpoint

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

Secondary Endpoints

- 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:

1. Percent decrease from baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation
2. 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
3. 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

Statistical Methods:

Safety: 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.

Summary Of Results:

Safety Results: There were no deaths, serious adverse events, or other significant AEs during this trial. The number of subjects with AEs while receiving OSB-IR was similar to the number of subjects with AEs while they were receiving Prilosec. There were no clinically significant changes from baseline in the physical examination findings, vital sign measurements, and laboratory results during this trial.

Pharmacokinetic Results: Omeprazole pharmacokinetic parameters were compared between OSB-IR and Prilosec administered premeal at steady state (Day 7).

Table I. 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	0.23	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	2640	-	-
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**

Source: Post-text Tables 15.4-7, 15.4-10.1, and 15.4-13.
* 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 limits of quantification after Dose 7 of Prilosec and is not included in the summary statistics for Prilosec; however, is 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 is ln[AUC(0-inf)] on Day 7.

The primary bioequivalence endpoint was AUC(0-inf) at steady state (Day 7). OSB-IR 40 mg and Prilosec 40 mg administered once a day in the morning were bioequivalent with respect to AUC as illustrated in Table I. The AUC(0-inf) 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 greater than for Prilosec with a mean ratio of 119.50% and 90% CI of 107.23% to 133.17%.

Table II. Summary of OSB-IR 40 mg Postmeal (Day 8) vs OSB-IR 40 mg Premeal (Day 7) Plasma Omeprazole Pharmacokinetic 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**

Source: Post-text Tables 15.4-8, 15.4-14, and 15.4-16.
* 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.

Administration of OSB-IR 40 mg at steady state 1 hour after initiation of a standardized high-fat breakfast reduced the bioavailability to 72.82% [percent mean ratio for AUC(0-inf)] of the premeal value as illustrated in Table II. The Cmax mean ratio (postmeal:premeal) was 40.25%. Food delayed the mean Tmax by 55 minutes.

Pharmacodynamic Results:

Table III. Assessment of Pharmacodynamic Equivalence Between OSB-IR 40 mg and Prilosec 40 mg for Integrated Gastric Acidity

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity	OSB-IR 40 mg			Prilosec 40 mg			% Mean Ratio **	90% CI for % Mean Ratio
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD		
Day 7	24	83.33	17.07	24	85.11	19.74	101.74	87.35-118.49

Source: Post-text Table 15.4-22.

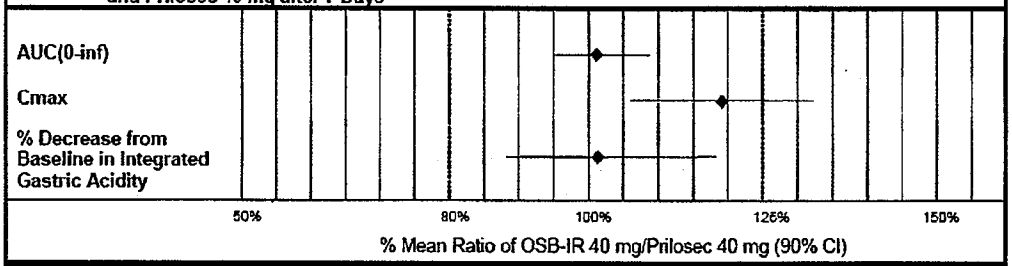
* When calculating the percent decrease from Baseline, Baseline is the mean of two baseline measurements.

** Differences in the percent decrease from Baseline for integrated gastric acidity for OSB-IR and Prilosec are assessed using an ANOVA model. Integrated gastric acidity is natural log transformed prior to the analysis. The 90% CI for treatment difference is calculated, and the log transformed values are reverse transformed, and multiplied by 100 to present confidence intervals about the treatment mean ratio on a percentage scale.
% Mean Ratio = 100 * exp(OSB-IR - Prilosec).

OSB-IR was pharmacodynamically equivalent to Prilosec at steady state (Day 7) with respect to the percent decrease from baseline in integrated gastric acidity (Table III). The boundaries of the 90% CIs were between 80% and 125% (87.35% to 118.49%).

CONCLUSION: OSB-IR and Prilosec were bioequivalent with regard to AUC(0-inf) and percent decrease from baseline in integrated gastric acidity for OSB-IR on Days 1 and 7. The two treatments were not bioequivalent with regard to Cmax, with the upper boundary of the confidence interval around the mean ratio slightly above the defined upper boundary for bioequivalence at steady state. This difference in Cmax had no apparent effect on the pharmacodynamics or safety of OSB-IR in this trial. The pharmacodynamic data show that both OSB-IR and Prilosec are equally effective in suppressing the production of gastric acid.

Figure I. Summary Assessments of Pharmacokinetic/Pharmacodynamic Bioequivalence for OSB-IR 40 mg and Prilosec 40 mg after 7 Days



The pharmacokinetic data obtained when OSB-IR was dosed following a standardized high-fat breakfast on Day 8 showed a decrease in bioavailability of omeprazole in the presence of food. The bioavailability of omeprazole from OSB-IR postmeal on Day 8, however, was greater than the bioavailability of omeprazole from Prilosec or from OSB-IR premeal on Day 1.

Both OSB-IR and Prilosec were well tolerated during the 7 to 8 day dosing periods in this trial. No meaningful differences were observed in the safety data between the two treatments.

3. OSB-IR-C06

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

Name of Sponsor: Santarus, Inc. **Name of Finished Product:** OSB-IR (Omeprazole Sodium Bicarbonate-Immediate Release) **Name of Active Ingredient:** Omeprazole	Individual Trial Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Trial: 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

Investigator: Mark J. Allison, MD
Trial Center: MDS Pharma Services, 4747 E. Beautiful Lane, Phoenix, AZ 85044

Publication (reference): None

Date of First Subject Enrollment: September 27, 2002 **Date of Last Subject Completed:** November 12, 2002	**Phase of Development:** I

Trial Objectives:

Primary Objective: The primary objective was to test the hypothesis that OSB-IR 20 mg is pharmacokinetically bioequivalent to Prilosec 20 mg.

Secondary Objectives: The secondary objectives were as follows:

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

Methodology: This was 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.

Safety assessments throughout this trial consisted of physical examination, vital sign measurements, clinical laboratory testing, monitoring for adverse events (AEs), and monitoring for use of concomitant medications.

Number of Subjects (planned and analyzed): Up to 36 subjects were to be enrolled to ensure that at least 24 subjects completed the trial with pharmacokinetic and pharmacodynamic data for Doses 1 and 7 of each of the two periods. Thirty-six subjects were dosed and 35 subjects completed the trial. Thirty-five subjects were included in the pharmacokinetic analysis and 28 subjects were included in the pharmacodynamic analyses for Doses 1 and 7.

Diagnosis and Main Criteria for Inclusion and Exclusion: Participants in this trial were healthy non-Asian subjects, males or nonlactating, nonpregnant females who were 18 to 45 years of age and between 120 and 200 pounds, and who satisfied all inclusion and exclusion criteria.

Test Product, Dose and Mode of Administration, Batch Number: OSB-IR 20 mg (Lot No. F1227A001) administered orally as a 20 mL aqueous suspension followed by 100 mL water once daily for eight consecutive days or once daily for seven consecutive days and twice daily on the eighth day.

Duration of Treatment: Subjects participated in this trial for up to 43 days (up to 14 days for screening, one 7-day and one 8-day treatment period, and a 10 to 14-day washout between periods).

Reference Product, Dose, and Mode of Administration, Batch Number: Prilosec® 20 mg (omeprazole, manufactured for AstraZeneca, Inc., by Merck & Co., Inc., Lot No. M1907Y) delayed-release, enteric-coated capsules, administered orally with 120 mL water once daily for seven consecutive days.

Criteria for Evaluation:

There were no efficacy measurements in this trial.

Safety: 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.

Pharmacokinetic Endpoints:

Primary Endpoint

The primary pharmacokinetic endpoint was 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 Endpoints

The secondary pharmacokinetic endpoints were as follows:

1. Peak plasma concentration (Cmax) after the seventh dose of each omeprazole formulation
2. AUC(0-inf) after the first dose of each omeprazole formulation
3. 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)]
4. All pharmacokinetic parameters obtained with OSB-IR 20 mg administered postmeal

Pharmacodynamic Endpoints:

Primary Endpoint

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

Secondary Endpoints

The secondary pharmacodynamic endpoints were as follows:

1. 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
2. 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
3. Median gastric pH and the percent time gastric pH was ≤ 4 for the 24-hour interval after dosing on Days 7 and 8 in Period 2

Statistical Methods:

Safety: 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.

SUMMARY OF RESULTS:

Safety Results: There were no deaths, serious adverse events, or other significant adverse events (AEs) during this trial. The number of subjects with AEs while receiving OSB-IR 20 mg was similar to the number of subjects with AEs while they were receiving Prilosec 20 mg. There were no clinically significant changes from baseline in the physical examination findings, vital sign measurements, or laboratory results during this trial.

Pharmacokinetic Results: Omeprazole pharmacokinetic parameters were compared between OSB-IR 20 mg and Prilosec 20 mg administered premeal at steady state (Day 7).

Table I. 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**

Source: Post-text Tables 15.4-7.1, 15.4-10, and 15.4-13.
* 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.

The primary bioequivalence endpoint was AUC(0-inf) at steady state (Day 7). Table I illustrates that OSB-IR 20 mg and Prilosec 20 mg administered once daily in the morning were bioequivalent with respect to AUC. The AUC(0-inf) least-squares means ratio was 106.71% with a 90% CI of 100.01% to 113.86%. The Cmax for OSB-IR 20 mg at steady state was greater than for Prilosec 20 mg (mean ratio of 157.02%, 90% CI of 141.50% to 174.24%).

Table II. 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

Source: Post-text Tables 15.4-8, 15.4-14, and 15.4-16.
* 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.

At steady state, administration of OSB-IR 20 mg 1 hour after the start of a standardized high-fat breakfast reduced the bioavailability to 76.08% [percent mean ratio for AUC(0-inf)] of the premeal value (Table II). Administration of OSB-IR 20 mg after the meal lowered the Cmax mean ratio (postmeal:premeal) to 36.91% and delayed the mean Tmax by 0.56 hours (34 minutes).

Pharmacodynamic Results:

Table III. Assessment of Pharmacodynamic Equivalence Between OSB-IR 20 mg and Prilosec 20 mg for Integrated Gastric Acidity

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity	OSB-IR 20 mg			Prilosec 20 mg			% Mean Ratio**	90% CI for % Mean Ratio**
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD		
Day 7	28	78.66	18.87	28	78.58	19.43	101.72	91.98 - 112.49

Source: Post-text Table 15.4-22.

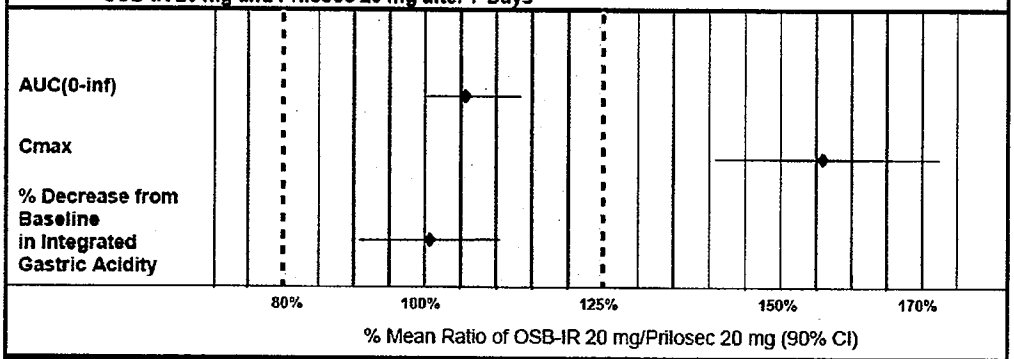
* When calculating the percent decrease from Baseline, Baseline is the corresponding baseline value for that period.

** Differences in the percent decrease from Baseline for integrated gastric acidity for OSB-IR and Prilosec are assessed using an ANOVA model. Integrated gastric acidity is natural log transformed prior to the analysis. The 90% CI for treatment difference is calculated, and the log transformed values are reverse transformed and multiplied by 100 to present confidence intervals about the treatment mean ratio on a percentage scale. % Mean Ratio = 100*exp(OSB-IR - Prilosec).

OSB-IR 20 mg was pharmacodynamically equivalent to Prilosec 20 mg at steady state (Day 7) with respect to the percent decrease from baseline in integrated gastric acidity (Table III). The boundaries of the 90% CI were between 80% and 125% (ie, 91.98% to 112.49%).

CONCLUSION: OSB-IR 20 mg was bioequivalent to Prilosec 20 mg with regard to AUC(0-inf) and percent decrease from baseline in integrated gastric acidity for on Day 7 (Figure 1). The two treatments were not bioequivalent with regard to Cmax, where the entire confidence interval around the mean ratio was above the defined upper boundary for bioequivalence at steady state. This difference in Cmax had no apparent effect on the pharmacodynamics or safety of OSB-IR 20 mg in this trial. The pharmacodynamic data show that both OSB-IR 20 mg and Prilosec 20 mg are equally effective in suppressing the production of gastric acid.

Figure I. Summary Assessments of Pharmacokinetic/Pharmacodynamic Bioequivalence for OSB-IR 20 mg and Prilosec 20 mg after 7 Days



The pharmacokinetic data obtained when OSB-IR was dosed following a standardized high-fat breakfast on Day 8 showed a decrease in bioavailability of omeprazole in the presence of food. The bioavailability of omeprazole from OSB-IR 20 mg postmeal on Day 8, however, was greater than the bioavailability of omeprazole from OSB-IR 20 mg or from Prilosec 20 mg premeal on Day 1.

Both OSB-IR 20 mg and Prilosec 20 mg were well tolerated during the 7-day to 8-day dosing periods in this trial. No meaningful differences between the treatments were observed with respect to safety.

4. Study OSB-IR-C07, entitled" A multicenter, open-label trial to evaluate the safety of OSB-IR 40 mg in patients with benigh gastric or duodenal ulcers, symptomatic gastroesophageal reflux disease or erosive esophagitis."

Name of Sponsor: Santarus, Inc. **Name of Finished Product:** OSB-IR 40 mg (Omeprazole Immediate-Release Suspension) **Name of Active Ingredient:** Omeprazole	Individual Trial Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Trial: A Multicenter, Open-Label Trial to Evaluate the Safety of OSB-IR 40 mg in Patients with Benign Gastric or Duodenal Ulcers, Symptomatic Gastroesophageal Reflux Disease or Erosive Esophagitis

Trial Number: OSB-IR-C07

Investigators (who enrolled patients): Charles Barish, MD, Eugene Bonapace, MD, Steven Duckor, MD, Madeline Dupree, MD, David Eskreis, MD, Syam Gaddam, MD, William Hirota, MD, Wieslaw Ignatowicz, MD, James Jones, MD, Charles King, MD, Richard Krause, MD, David Miller, MD, Rao Movva, MD, Daniel Pambianco, MD, Ronald Pruitt, MD, Dennis Riff, MD, Alan Safdi, MD, Howard Schwartz, MD, Lawrence Wruble, MD

Trial Sites: Patients were enrolled at 19 sites across the United States.

Publications (references): None at the time of this report.

Date of First Patient Enrollment: October 20, 2003 **Date of Last Patient Completed:** February, 23, 2004	**Phase of Development:** 3

Trial Objectives: The objective of this trial was to assess the safety profile of OSB-IR 40 mg in patients diagnosed with benign gastric ulcers (GU) or duodenal ulcers (DU), symptomatic gastroesophageal reflux disease (GERD), or erosive esophagitis (EE).

Methodology: This was a multicenter, open-label, prospective clinical trial evaluating the safety of OSB-IR 40 mg administered once daily for 8 weeks to patients with benign GU or DU, symptomatic GERD, or EE. Esophagogastroduodenoscopy (EGD) was required to document a diagnosis of benign GU unless the EGD had been performed in the 2-week interval prior to Day 0. An EGD was also required in patients with a diagnosis of Barrett's esophagus if a surveillance endoscopy and biopsies had not been performed in the year prior to screening for this trial. An EGD was not required to confirm a diagnosis of DU, symptomatic GERD, or EE. Biopsy and cytology results from screening EGDs were to be available by Day 0.

Prior to dispensing trial drug, all patients were to have a medical history taken, to undergo a physical exam, to have blood samples taken for hematology and chemistry tests, and to provide a urine sample to test for glucose and protein. A blood sample was to be collected from women of childbearing potential to measure serum human chorionic gonadotropin (hCG) levels.

After screening patients were to return to the trial site on Day 0, at which time trial drug was to be dispensed. Patients were to be instructed to take the trial drug within 30 to 60 minutes prior to breakfast starting the next day (Trial Day 1) and continuing daily for 8 weeks. If the patients were not eating breakfast, trial drug was to be taken between 6 AM and 9 AM. Patients were supplied with Gelusil® Tablets to be used as rescue medication if symptoms were not adequately controlled by trial medication. Up to 12 Gelusil Tablets per day were allowed. Patients were to return for clinic visits at Week 2 (Day 14 ± 3), Week 4 (Day 28 ± 3), and one day after completing 8 weeks of treatment (Day 57 ± 3).

Name of Sponsor: Santarus, Inc. **Name of Finished Product:** OSB-IR 40 mg (Omeprazole Immediate-Release Suspension) **Name of Active Ingredient:** Omeprazole	Individual Trial Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

There were no efficacy assessments in this trial. Safety assessments were based on laboratory test results, physical examinations, and on the occurrence, and severity of adverse events (AEs). In addition, a telephone call was to be made to the investigator 30 days after the last dose of trial drug to query for the occurrence of SAEs.

A patient was considered to have completed the trial if he/she completed 8 weeks of treatment.

Number of Patients (planned and analyzed): Enrollment of approximately 250 patients was planned (including at least 50 to 75 patients with GU). A total of 243 patients were enrolled in the trial. There were 97 GU patients and 146 patients diagnosed with DU, GERD, or EE.

Diagnosis and Main Criteria for Inclusion and Exclusion: Patients enrolled in this trial were to be at least 18 years of age with a diagnosis of a benign GU or DU, symptomatic GERD, or EE.

Test Product, Dose and Mode of Administration, Batch Number: OSB-IR 40 mg oral suspension (Lot Number F1020A003) was provided to patients as single-use individual packets containing 6.2 grams of OSB-IR formulation (40 mg of omeprazole). The packet contents were to be mixed with water in a cup that was provided to patients. The patients were to take the trial drug within 30 to 60 minutes prior to breakfast beginning on Trial Day 1. If the patients did not eat breakfast, they were to take the drug between 6 AM and 9 AM.

Duration of Treatment: Each patient received trial drug for a maximum of 8 weeks (± 3 days).

Criteria for Evaluation:

Efficacy: Efficacy was not assessed in this trial.

Safety: Safety was assessed by evaluating the occurrence, severity, and relationship to trial drug of AEs and SAEs, laboratory test results, and changes in physical examination findings from the Screening Visit to the Final Visit.

Statistical Methods:

Analysis Sets: Analyses of safety included all patients treated with at least one dose of OSB-IR 40 mg.

Efficacy: No analyses of efficacy were performed in this trial.

Safety: Descriptive statistics were used to summarize safety parameters.

Summary of Results:

Demographics and Baseline Disease Characteristics:

Efficacy Results:

There were no evaluations of efficacy in this trial.

Safety Results:

A total of 243 patients with benign GU or DU, symptomatic GERD, or EE received at least one dose of OSB-IR 40 mg in this trial, with 225 patients (92.6%) completing 8 weeks of treatment.

Adverse events were experienced by 130 patients (53.5%). Adverse events considered to be related to OSB-IR 40 mg were experienced by 33 patients (13.6%), with the most frequently reported

Name of Sponsor: Santarus, Inc.	Individual Trial Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: OSB-IR 40 mg (Omeprazole Immediate-Release Suspension)		
Name of Active Ingredient: Omeprazole		

drug-related AEs involving gastrointestinal disorders (28 patients; 11.5%).

One patient died suddenly during the trial as the result of coronary artery disease. This death was not related to OSB-IR 40 mg. Serious AEs were experienced by 8 patients during the trial. None of these SAEs were considered to be related to OSB-IR 40 mg.

The clinical laboratory test results were normal at Baseline and the Final Visit for the majority of patients. Similarly, the findings of the physical examinations at the Final Visit were unchanged from those at Baseline for the majority of patients.

Overall, OSB-IR 40 mg was well tolerated during this 8-week trial in patients with benign GU, DU, symptomatic GERD, or EE.

Conclusions:

- More than 200 patients completed 8 weeks of treatment and were compliant with the daily regimen of OSB-IR oral suspension 40 mg.
- OSB-IR oral suspension 40 mg was well tolerated by patients with acid-related conditions over 8 weeks of treatment.
- The safety profile of OSB-IR oral suspension 40 mg was similar to that described for Prilosec in the Prilosec labeling.

5. **Trial Number: OME-IR(TAB)-C01**

A COMPARISON OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF OMEPRAZOLE IMMEDIATE-RELEASE CHEWABLE TABLETS 20 MG WITH PRILOSEC® DELAYED-RELEASE CAPSULES 20 MG IN HEALTHY SUBJECTS

Name of Sponsor: Santarus, Inc.	*(For National Authority Use Only)*
Name of Finished Product: Zegerid® (omeprazole) Chewable Tablets 20 mg	
Name of Active Ingredient: Omeprazole	
Title of Trial: A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid® Immediate-Release Chewable Tablets 20 mg with Prilosec® Delayed-Release Capsules 20 mg in Healthy Subjects	
Investigator: Gaetano Morelli, MD **Trial Center:** MDS Pharma Services, 2350 Cohen Street, Saint-Laurent (Montréal), Québec H4R 2N6, Canada	
Publication (reference): None	
Date of First Subject Dosed: October 2, 2004 **Date of Last Subject Completed:** November 1, 2004	**Phase of Development:** 1

Trial Objectives:

Primary Objective: The primary objective was to test the hypothesis that Zegerid® Chewable Tablets 20 mg are pharmacokinetically bioequivalent to Prilosec® Delayed-Release Capsules 20 mg with respect to area under the curve (AUC).

Secondary Objectives: The secondary objectives were:

1. To assess whether Zegerid® Chewable Tablets 20 mg are pharmacodynamically bioequivalent to Prilosec Delayed-Release Capsules 20 mg with respect to percent decrease from Baseline in integrated gastric acidity, and
2. To compare the pharmacokinetics of Zegerid® Chewable Tablets 20 mg administered postmeal to the pharmacokinetics of Zegerid® Chewable Tablets 20 mg administered premeal.

Methodology: This was an open-label, randomized, 2-period crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of seven consecutive daily doses of Zegerid® Chewable Tablets 20 mg compared to seven consecutive daily doses of Prilosec 20 mg in healthy subjects. A comparison of pharmacokinetic parameters for Zegerid®, administered before versus after a meal, was also conducted.

Volunteers were screened within 21 days before baseline measurements (eg, gastric pH, vital signs). Gastric pH was recorded for 24 hours before the first dose of trial drug. In Period 1, subjects received Zegerid® Chewable Tablets 20 mg or Prilosec 20 mg, as randomized, 1 hour before a standardized high-fat breakfast for 7 consecutive days. Blood samples were collected for 12 hours to determine plasma omeprazole concentrations and gastric pH levels were recorded for 24 hours after the doses on Days 1 and 7. Subjects who received Zegerid® 20 mg in Period 1 were given an eighth dose on Day 8 in Period 1, 1 hour after the start of the standardized high-fat 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 that no eighth dose of Zegerid® was given.

Safety assessments throughout this trial consisted of physical examinations, vital sign measurements, clinical laboratory tests, adverse events (AEs) and serious adverse events (SAEs).
Number of Subjects (planned and analyzed): Up to 36 subjects were to be enrolled to ensure that at least 24 subjects completed the trial with pharmacokinetic and pharmacodynamic data for Doses 1 and 7 in each of the two periods, and to ensure that at least 12 of the enrolled subjects completed the eighth treatment day with Zegerid® Chewable Tablets 20 mg during Period 1. Thirty-five subjects were dosed and 34 subjects completed the trial. Thirty-four subjects were included in the pharmacokinetic analyses and 29 subjects were included in the pharmacodynamic analyses for Days 1 and 7. Sixteen subjects were included in the postmeal (Day 8) versus premeal (Day 7) analysis.
Diagnosis and Main Criteria for Inclusion and Exclusion: Participants in this trial were healthy non-Asian (male and nonlactating, nonpregnant female) subjects who were 18 to 45 years of age and between 120 and 200 pounds, and who also satisfied all other inclusion and exclusion criteria.
Test Drug, Dose and Mode of Administration, Batch Number: Zegerid® Chewable Tablets 20 mg (Lot 3040892) were to be administered orally once daily for 8 consecutive days in one half of the subjects and once daily for 7 consecutive days in the other half.
Duration of Participation: Including screening, subjects participated in this trial for up to 39 days.
Reference Drug, Dose and Mode of Administration, Batch Number: Prilosec® 20 mg (omeprazole, manufactured for AstraZeneca, Inc., by Merck & Co., Inc., Lot N2058) delayed-release capsules containing omeprazole as enteric-coated granules, were administered orally with 120 mL water once daily for 7 consecutive days.
Criteria for Evaluation: **Efficacy:** Except for the pharmacodynamic evaluations discussed below, efficacy was not evaluated in this trial. **Safety:** The severity and relationship to trial drug of AEs and SAEs 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.

Pharmacokinetic Endpoints:

Primary Endpoint

The primary pharmacokinetic endpoint was the bioavailability of omeprazole [AUC(0-inf)] after the seventh dose of each omeprazole formulation.

Secondary Endpoints

The secondary pharmacokinetic endpoints were as follows:

1. Peak plasma concentration (Cmax) after the seventh dose of each omeprazole formulation
2. AUC(0-inf) and Cmax after the first dose of each omeprazole formulation
3. 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 time-concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)]
4. All pharmacokinetic parameters obtained with Zegerid® Chewable Tablets 20 mg administered postmeal

Pharmacodynamic Endpoints:

Primary Endpoint

The primary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation.

Secondary Endpoint

The secondary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the first dose of each omeprazole formulation.

Other Pharmacodynamic Parameters (24-hour postdose intervals)

- Mean gastric acid concentration (mM)
- Median gastric pH
- Percentage of time with gastric pH ≤ 4

Statistical Methods:

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

Pharmacokinetics: Pharmacokinetic parameters were evaluated using standard criteria for bioequivalence. An analysis of variance (ANOVA) model was used to test the bioequivalence of Zegerid® Chewable Tablets and Prilosec Delayed-Release Capsules, using the natural logarithmic transformation of AUC(0-inf) and Cmax. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. With respect to AUC(0-inf) and Cmax, equivalence was to be declared for each parameter if the bounds of the 90% CIs for the percent mean ratio, Zegerid / Prilosec, were between 80% and 125%.

Pharmacodynamics: Pharmacodynamic parameters were evaluated using the standard bioequivalence methodology for pharmacokinetic parameters. Baseline values for integrated gastric acidity were first compared between the two treatment periods using an ANOVA model. If there was no statistically significant difference in baseline values for integrated gastric acidity, the baseline values for the two periods were to be averaged when calculating change from Baseline; otherwise, the corresponding baseline value for that period was to be used. The analysis of integrated gastric acidity for the 24-hour period following dosing was conducted on the percent decrease from Baseline on Days 1 and 7 calculated for each subject as 100 x [Baseline – Day 1 (or Day 7)]/Baseline.

An ANOVA model was used to test the pharmacodynamic equivalence of Zegerid® Chewable Tablets and Prilosec Delayed-Release Capsules, using the natural logarithmic transformation of percent decrease from Baseline in integrated gastric acidity. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. Pharmacodynamic equivalence was to be declared if the bounds of the 90% CIs for the percent mean ratio of percent decrease from Baseline in integrated gastric acidity, Zegerid / Prilosec, were between 80% and 125%.

Summary of Results:

Safety Results: There were no deaths, SAEs, or other AEs of clinical importance during this trial. There were no notable differences in incidence and nature of the AEs for the two treatments. There were no clinically significant changes from Baseline in the physical examination findings, vital sign measurements, or laboratory results during this trial.

Pharmacokinetic Results: The comparison of pharmacokinetic parameters for Zegerid® Chewable Tablets 20 mg and Prilosec 20 mg, administered premeal at steady state (Day 7), are presented in Table I.

Table I. Summary of Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid® (TAB) 20 mg and Prilosec 20 mg Administered Premeal

	Plasma Omeprazole							
	Zegerid(TAB) 20 mg			Prilosec 20 mg				
Parameters*	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	34	769.1	360.3	34	583.1	303.8		
Tmax (hr)	34	0.71	0.46	34	1.50	0.50		
AUC (0-t) (ng*hr/mL)	34	1346	859.8	34	1185	867.3		
AUC (0-inf) (ng*hr/mL)	34	1359	873.8	34	1202	889.6		
T½ (hr)	34	1.01	0.39	34	1.05	0.36		
Kel (1/hr)	34	0.78	0.29	34	0.73	0.21		
ln (Cmax)	34	6.54	0.46	34	6.26	0.47	133.42	118.49 - 150.24
ln [AUC(0-t)]	34	7.03	0.61	34	6.89	0.61	115.37	106.88 - 124.53
ln [AUC(0-inf)]	**34**	**7.04**	**0.61**	**34**	**6.90**	**0.61**	**114.93**	**106.45 - 124.07**

Source: Post-text Tables 15.4-7, 15.4-10 and 15.4-13.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

Note: Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.

Table I shows that Zegerid® Chewable Tablets 20 mg and Prilosec 20 mg administered once daily before breakfast were equivalent with respect to AUC(0-inf). The percent mean ratio of AUC(0-inf), Zegerid / Prilosec, was 114.93%; 90% CI 106.45% – 124.07%. The Cmax for Zegerid® 20 mg at steady state was greater than for Prilosec 20 mg (percent mean ratio of 133.42%, 90% CI 118.49% – 150.24%). The Tmax was significantly shorter for Zegerid® 20 mg than for Prilosec 20 mg ($p<0.001$).

Table II. Summary of Day 8 and Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid® (TAB) 20 mg Administered Postmeal vs. Premeal

	Plasma Omeprazole							
	Zegerid (TAB) 20 mg (Postmeal)			Zegerid (TAB) 20 mg (Premeal)				
Parameters*	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	16	417.2	226.7	16	930.5	385.0		
Tmax (hr)	16	0.99	0.68	16	0.66	0.45		
AUC (0-t) (ng*hr/mL)	16	1322	901.5	16	1708	1038		
AUC (0-inf) (ng*hr/mL)	16	1351	937.2	16	1726	1059		
T½ (hr)	16	1.39	0.46	16	1.14	0.45		
Kel (1/hr)	16	0.54	0.13	16	0.69	0.23		
ln (Cmax)	16	5.88	0.60	16	6.77	0.38	41.37	33.06 - 51.77
ln [AUC(0-t)]	16	7.00	0.63	16	7.30	0.55	74.62	67.30 - 82.72
ln [AUC(0-inf)]	16	7.02	0.63	16	7.30	0.55	75.48	68.24 - 83.48

Source: Post-text Tables 15.4-8, 15.4-14 and 15.4-16.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

** All subjects who received who completed both 7-day omeprazole treatments Dose 8 of Zegerid 20 mg after a meal in Period 1 were included in the analysis.

Ingestion of Zegerid® Chewable Tablets 20 mg 1 hour after a standardized high-fat breakfast decreased the total bioavailability of omeprazole by 25% (percent mean ratio, 75.48%) compared to premeal; it lowered the Cmax of omeprazole by 59% (percent mean ratio, 41.37%) and delayed the mean Tmax by 0.33 hours (20 minutes).

Pharmacodynamic Results:

Table III. Assessment of Pharmacodynamic Equivalence between Zegerid® (TAB) 20 mg and Prilosec 20 mg for Integrated Gastric Acidity

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity	Zegerid(TAB) 20 mg			Prilosec 20 mg			% Mean Ratio	90% CI
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
Day 7	29	68.98	19.45	29	67.06	21.98	107.01	95.24 - 120.25

Source: Post-text Tables 15.4-21 and 15.4-22.

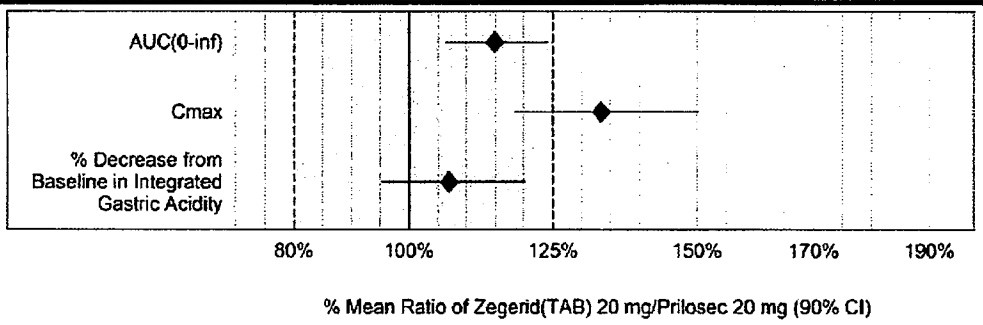
* When calculating the percent decrease from Baseline, the mean of Period 1 and Period 2 baseline measurements was used.

Note: Percent mean ratio and 90% confidence interval (CI) were based on least-squares means.

Zegerid® Chewable Tablets 20 mg were pharmacodynamically equivalent to Prilosec Delayed-Release Capsules 20 mg at steady state (Day 7) with respect to the percent decrease from Baseline in integrated gastric acidity (Table III). The bounds of the 90% CI for the percent mean ratio were between 80% and 125%.

Conclusion: Zegerid® Chewable Tablets 20 mg were equivalent to Prilosec Delayed-Release Capsules 20 mg with regard to AUC(0-inf) and percent decrease from Baseline in integrated gastric acidity on Day 7 (Figure I). The two treatments were not equivalent with regard to Cmax. This difference in Cmax had no apparent effect on the pharmacodynamics or safety of Zegerid® 20 mg in this trial. The pharmacodynamic data show that both Zegerid® Chewable Tablets 20 mg and Prilosec Capsules 20 mg are equally effective in decreasing integrated gastric acidity at steady state.

Figure I. Summary Assessment of Pharmacokinetic/Pharmacodynamic Bioequivalence for Zegerid® (TAB) 20 mg and Prilosec 20 mg After 7 Days



Source: Post-text Tables 15.4-13 and 15.4-22.

The pharmacokinetic data showed a 25% decrease in bioavailability of omeprazole in the presence of food when Zegerid® Chewable Tablets 20 mg were given following a standardized high-fat breakfast on Day 8.

Both Zegerid® Chewable Tablets 20 mg and Prilosec Delayed-Release Capsules 20 mg were well tolerated during the 7- to 8-day dosing periods in this trial. No meaningful differences between the treatments were observed with respect to safety.

6.. **Trial Number: OME-IR(TAB)-C02**

A COMPARISON OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF OMEPRAZOLE IMMEDIATE-RELEASE CHEWABLE TABLETS 40 MG WITH PRILOSEC® DELAYED-RELEASE CAPSULES 40 MG IN HEALTHY SUBJECTS

Name of Sponsor: Santarus, Inc.	*(For National Authority Use Only)*
Name of Finished Product: Zegerid® (omeprazole) Chewable Tablets 40 mg	
Name of Active Ingredient: Omeprazole	

Title of Trial: A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid® Immediate-Release Chewable Tablets 40 mg with Prilosec® Delayed-Release Capsules 40 mg in Healthy Subjects

Investigator: Gaetano Morelli, MD
Trial Center: MDS Pharma Services, 2350 Cohen Street, Saint-Laurent (Montréal), Québec H4R 2N6, Canada

Publication (reference): None

Date of First Subject Dosed: November 4, 2004 **Date of Last Subject Completed:** December 11, 2004	**Phase of Development:** 1

Trial Objectives:

Primary Objective: The primary objective was to test the hypothesis that Zegerid® Chewable Tablets 40 mg are pharmacokinetically bioequivalent to Prilosec® Delayed-Release Capsules 40 mg with respect to area under the curve (AUC).

Secondary Objectives: The secondary objectives were:

1. To assess whether Zegerid® Chewable Tablets 40 mg are pharmacodynamically bioequivalent to Prilosec Delayed-Release Capsules 40 mg with respect to percent decrease from Baseline in integrated gastric acidity, and
2. To compare the pharmacokinetics of Zegerid® Chewable Tablets 40 mg administered postmeal to the pharmacokinetics of Zegerid® Chewable Tablets 40 mg administered premeal

Methodology: This was an open-label, randomized, 2-period crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of seven consecutive daily doses of Zegerid® Chewable Tablets 40 mg compared to seven consecutive daily doses of Prilosec 40 mg in healthy subjects. A comparison of pharmacokinetic parameters for Zegerid®, administered before versus after a meal, was also conducted.

Volunteers were screened within 21 days before baseline measurements (eg, gastric pH, vital signs). Gastric pH was recorded for 24 hours before the first dose of trial drug. In Period 1, subjects received Zegerid® Chewable Tablets 40 mg or Prilosec 40 mg, as randomized, 1 hour before a standardized high-fat breakfast for 7 consecutive days. Blood samples were collected for 12 hours to determine plasma omeprazole concentrations and gastric pH levels were recorded for 24 hours after the doses on Days 1 and 7. Subjects who received Zegerid® 40 mg in Period 1 were given an eighth dose on Day 8 in Period 1, 1 hour after the start of the standardized high-fat 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 that no eighth dose of Zegerid® 40 mg was given.

Safety assessments throughout this trial consisted of physical examinations, vital sign measurements, clinical laboratory tests, adverse events (AEs) and serious adverse events (SAEs).
Number of Subjects (planned and analyzed): Up to 36 subjects were to be enrolled to ensure that at least 24 subjects completed the trial with pharmacokinetic and pharmacodynamic data for Doses 1 and 7 in each of the two periods, and to ensure that at least 12 of the enrolled subjects completed the eighth treatment day with Zegerid® Chewable Tablets 40 mg during Period 1. Thirty-six subjects were dosed and 35 subjects completed the trial. Thirty-five subjects were included in both the pharmacokinetic analyses and in the pharmacodynamic analyses for Days 1 and 7. Seventeen subjects were included in the postmeal (Day 8) versus premeal (Day 7) analysis.
Diagnosis and Main Criteria for Inclusion and Exclusion: Participants in this trial were healthy non-Asian (male and nonlactating, nonpregnant female) subjects who were 18 to 45 years of age and between 120 and 200 pounds, and who also satisfied all other inclusion and exclusion criteria.
Test Drug, Dose and Mode of Administration, Batch Number: Zegerid® Chewable Tablets 40 mg (Lot No. 3040893) were to be administered orally once daily for 8 consecutive days in one half of the subjects and once daily for 7 consecutive days in the other half.
Duration of Participation: Including screening, subjects participated in this trial for up to 55 days.
Reference Drug, Dose and Mode of Administration, Batch Number: Prilosec® 40 mg (omeprazole, manufactured for AstraZeneca, Inc., by Merck & Co., Inc., Lot No. N2815) delayed-release capsules containing omeprazole as enteric-coated granules, were administered orally with 120 mL water once daily for 7 consecutive days.
Criteria for Evaluation: **Efficacy:** Except for the pharmacodynamic evaluations discussed below, efficacy was not evaluated in this trial. **Safety:** The severity and relationship to trial drug of AEs and SAEs 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.

Pharmacokinetic Endpoints:

Primary Endpoint

The primary pharmacokinetic endpoint was the bioavailability of omeprazole [AUC(0-inf)] after the seventh dose of each omeprazole formulation.

Secondary Endpoints

The secondary pharmacokinetic endpoints were as follows:

1. Peak plasma concentration (Cmax) after the seventh dose of each omeprazole formulation
2. AUC(0-inf) and Cmax after the first dose of each omeprazole formulation
3. 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 time-concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)]
4. All pharmacokinetic parameters obtained with Zegerid® Chewable Tablets 40 mg administered postmeal

Pharmacodynamic Endpoints:

Primary Endpoint

The primary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation.

Secondary Endpoint

The secondary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the first dose of each omeprazole formulation.

Other Pharmacodynamic Parameters (24-hour postdose intervals)

- Mean gastric acid concentration (mM)
- Median gastric pH
- Percentage of time with gastric pH ≤ 4

Statistical Methods:

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

Pharmacokinetics: Pharmacokinetic parameters were evaluated using standard criteria for bioequivalence. An analysis of variance (ANOVA) model was used to test the bioequivalence of Zegerid® Chewable Tablets and Prilosec, using the natural logarithmic transformation of AUC(0-inf) and Cmax. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. With respect to AUC(0-inf) and Cmax, equivalence was to be declared for each parameter if the bounds of the 90% CIs for the percent mean ratio, Zegerid / Prilosec, were between 80% and 125%.

Pharmacodynamics: Pharmacodynamic parameters were evaluated using the standard bioequivalence methodology for pharmacokinetic parameters. Baseline values for integrated gastric acidity were first compared between the two treatment periods using an ANOVA model. If there was no statistically significant difference in baseline values for integrated gastric acidity, the baseline values for the two periods were to be averaged when calculating change from Baseline; otherwise, the corresponding baseline value for that period was to be used. The analysis of integrated gastric acidity for the 24-hour period following dosing was conducted on the percent decrease from Baseline on Days 1 and 7 calculated for each subject as 100 x [Baseline – Day 1 (or Day 7)]/Baseline.

An ANOVA model was used to test the pharmacodynamic equivalence of Zegerid® Chewable Tablets and Prilosec, using the natural logarithmic transformation of percent decrease from Baseline in integrated gastric acidity. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. Pharmacodynamic equivalence was to be declared if the bounds of the 90% CIs for the percent mean ratio of percent decrease from Baseline in integrated gastric acidity, Zegerid / Prilosec, were between 80% and 125%.

Summary of Results:

Safety Results: There were no deaths, SAEs, or other AEs of clinical importance during this trial. There were no notable differences in nature and incidence of the AEs for the two treatments. There were no clinically significant changes from Baseline in the physical examination findings, vital sign measurements, or laboratory results during this trial.

Pharmacokinetic Results: The comparison of pharmacokinetic parameters for Zegerid® Chewable Tablets 40 mg and Prilosec 40 mg, administered premeal at steady state (Day 7), are presented in Table I.

Table I. Summary of Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid®(TAB) 40 mg and Prilosec 40 mg Administered Premeal

	Plasma Omeprazole							
	Zegerid(TAB) 40 mg			Prilosec 40 mg				
Parameters*	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	35	1763	448.5	35	1417	497.1		
Tmax (hr)	35	0.77	0.44	35	1.51	0.74		
AUC (0-t) (ng•hr/mL)	35	4120	1886	35	3760	2044		
AUC (0-inf) (ng•hr/mL)	35	4168	1951	35	3837	2173		
T½ (hr)	35	1.36	0.48	35	1.45	0.57		
Kel (1/hr)	35	0.58	0.22	35	0.55	0.22		
ln (Cmax)	35	7.44	0.27	35	7.18	0.42	129.96	118.83 - 142.12
ln [AUC(0-t)]	35	8.21	0.52	35	8.08	0.59	113.92	107.20 - 121.05
ln [AUC(0-inf)]	**35**	**8.22**	**0.52**	**35**	**8.09**	**0.60**	**113.41**	**106.68 - 120.57**

Source: Post-text Tables 15.4-7, 15.4-10 and 15.4-13.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

Note: Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.

Table I shows that Zegerid® Chewable Tablets 40 mg and Prilosec 40 mg administered once daily before breakfast were equivalent with respect to AUC(0-inf). The percent mean ratio of AUC(0-inf), Zegerid / Prilosec, was 113.41%; 90% CI 106.68% – 120.57%. The Cmax for Zegerid® 40 mg at steady state was greater than for Prilosec 40 mg (percent mean ratio of 129.96%, 90% CI 118.83% – 142.12%). The Tmax was significantly shorter for Zegerid® 40 mg than for Prilosec 40 mg ($p<0.001$).

Table II. Summary of Day 8 and Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid®(TAB) 40 mg Administered Postmeal vs. Premeal

	Plasma Omeprazole							
	Zegerid(TAB) 40 mg (Postmeal)			Zegerid(TAB) 40 mg (Premeal)				
Parameters*	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	17	842.5	428.4	17	1862	543.5		
Tmax (hr)	17	1.22	0.61	17	0.65	0.30		
AUC (0-t) (ng•hr/mL)	17	3450	1860	17	4190	1949		
AUC (0-inf) (ng•hr/mL)	17	3499	1912	17	4232	1996		
T½ (hr)	17	1.56	0.35	17	1.40	0.46		
Kel (1/hr)	17	0.46	0.09	17	0.57	0.25		
ln (Cmax)	17	6.62	0.52	17	7.49	0.31	41.93	36.41 - 48.28
ln [AUC(0-t)]	17	7.98	0.65	17	8.21	0.57	79.25	75.27 - 83.45
ln [AUC(0-inf)]	17	7.99	0.65	17	8.22	0.58	79.62	75.71 - 83.73

Source: Post-text Tables 15.4-8, 15.4-14 and 15.4-16.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

** All subjects who completed both 7-day omeprazole treatments and received Dose 8 of Zegerid 40 mg after a meal in Period 1 were included in the analysis.

Note: Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.

Ingestion of Zegerid® Chewable Tablets 40 mg 1 hour after a standardized high-fat breakfast decreased the total bioavailability of omeprazole by 20% (percent mean ratio, 79.62%) compared to premeal; it lowered the Cmax of omeprazole by 58% (percent mean ratio, 41.93%) and delayed the mean Tmax by 0.57 hours (34 minutes).

Pharmacodynamic Results:

Table III. Assessment of Pharmacodynamic Equivalence between Zegerid® (TAB) 40 mg and Prilosec 40 mg for Integrated Gastric Acidity

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity	Zegerid(TAB) 40 mg			Prilosec 40 mg			% Mean Ratio	90% CI
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
Day 7	35	77.48	14.81	35	77.84	15.95	99.98	95.52 - 104.65

Source: Post-text Tables 15.4-21 and 15.4-22.

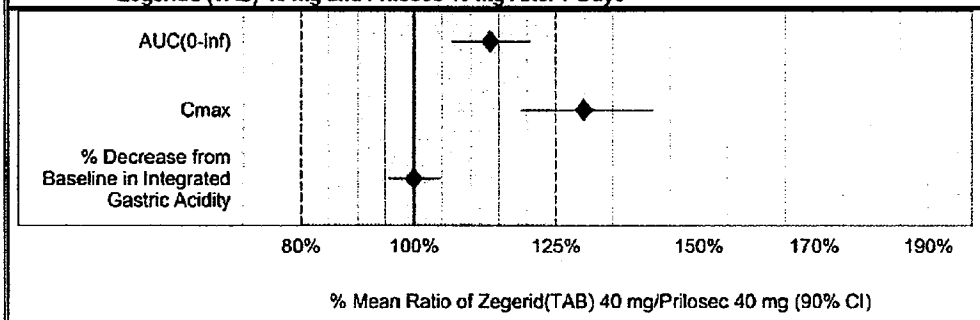
* When calculating the percent decrease from Baseline, the mean of Period 1 and Period 2 baseline measurements was used.

Note: Percent mean ratio and 90% confidence interval (CI) were based on least-squares means.

Zegerid® Chewable Tablets 40 mg were pharmacodynamically equivalent to Prilosec Capsules 40 mg at steady state (Day 7) with respect to the percent decrease from Baseline in integrated gastric acidity (Table III). The bounds of the 90% CI for the percent mean ratio were between 80% and 125%.

Conclusion: Zegerid® Chewable Tablets 40 mg were equivalent to Prilosec Capsules 40 mg with regard to AUC(0-inf) and percent decrease from Baseline in integrated gastric acidity on Day 7 (Figure I). The two treatments were not equivalent with regard to Cmax. This difference in Cmax had no apparent effect on the pharmacodynamics or safety of Zegerid® 40 mg in this trial. The pharmacodynamic data show that both Zegerid® Chewable Tablets 40 mg and Prilosec Capsules 40 mg are equally effective in decreasing integrated gastric acidity at steady state.

Figure I. Summary Assessment of Pharmacokinetic/Pharmacodynamic Bioequivalence for Zegerid® (TAB) 40 mg and Prilosec 40 mg After 7 Days



Source: Post-text Tables 15.4-13 and 15.4-22.

The pharmacokinetic data showed a 20% decrease in bioavailability of omeprazole in the presence of food when Zegerid® Chewable Tablets 40 mg were given following a standardized high-fat breakfast on Day 8.

Both Zegerid® Chewable Tablets 40 mg and Prilosec Delayed-Release Capsules 40 mg were well tolerated during the 7- to 8-day dosing periods in this trial. No meaningful differences between the treatments were observed with respect to safety.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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/s/

PEIFAN J BAI
11/02/2009

SUE CHIH H LEE
11/04/2009
At this time, it appears that the proposed brand name of Zegerid [redacted] is not acceptable to DMEPA. b(4)

BIOPHARMACEUTICS REVIEW

NDA#	22456
Drug	Omeprazole Sodium bicarbonate Magnesium hydroxide
Type	waiver request
Sponsor	Santarus
Letter Date	June 3, 2009
Reviewer	Patrick Marroum, Ph.D.

Background:

In this submission the sponsor is requested a biowaiver for an additional 20 mg strength The new strength meets the 2nd definition of proportionally similar as defined in the general BA/BE guidance.

RECOMMENDATION:

Since the new 20 mg strength meets the definition of proportionally similar, a bioequivalence/bioavailability waiver can be granted based on comparability of dissolution profiles in three media (0.1 N HCl and phosphate buffer pH 4.5 and 6.8) to the 40 mg strength that was tested in the bioequivalence study.

Patrick Marroum, Ph. D.
Office of New Drug Quality Assessment

CC: Kowblansky, Dorantes

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22456	ORIG 1	SANTARUS	ZEGERID

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/s/

PATRICK J MARROUM
08/10/2009

Cover Sheet and OCP Filing/Review Form

OFFICE OF CLINICAL PHARMACOLOGY

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	NDA 22-456	Brand Name	Zegerid®
OCP Division (I, II, III)	III	Generic Name	Omeprazole
Medical Division	Gastroenterology	Drug Class	Proton pump inhibitor
OCP Reviewers	PeiFan Bai	Indication(s)	Active duodenal ulcer
OCP Team Leader	Sue-Chih Lee	Dosage Form	Tablets
Date of Submission	Jan 28, 2009	Proposed Dosing Regimen	Tablets should be taken on an empty stomach at least one hour before a meal.
Estimated Due Date of OCP Review	Oct 4, 2009	Route of Administration	oral
Medical Division Due Date		Sponsor	Santarus, Inc
PDUFA Due Date	Dec 4, 2009	Priority Classification	standard

Clin. Pharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x	[redacted]	[redacted]	
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]		
1.1. *HEALTHY VOLUNTEERS-*				
single dose:	X	1		BE
multiple dose:	X	4		PK/PD
1.1.1. PATIENTS-				
single dose:				
multiple dose:	X	1	1	Safety
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	5		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**single**	1		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		6	6	

Filability and QBR comments

	"X" if yes	***Comments***
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• **What are the design features of the submitted studies used to support the labeling claims and fulfillment of PWR?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Jane Bai
4/3/2009 01:20:44 PM
BIOPHARMACEUTICS

Sue Chih Lee
4/3/2009 06:19:00 PM
BIOPHARMACEUTICS