CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-849 (SN-000)
Brand Name:	Zegerid
Generic Name:	Omeprazole
Dosage form and Strength:	20 and 40 mg Capsules
Route of administration:	Oral
Indication:	Related to GI disorders
Sponsor:	Santarus, Inc.
Type of submission:	Original
Clinical Division:	GI and Dermatology Division
OCPB Division:	DCPB III
Priority:	Standard
Submission date:	04/26/05, 01/04/06
OCPB Consult date:	05/10/05
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Edward D. Bashaw, Pharm. D.

I. Executive Summary

Omeprazole is a substituted benzimidazole that inhibits gastric acid secretion via specific inhibition of H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Omeprazole has been approved and marketed in the US since 1989 as Prilosec delayed release (DR) 20 and 40 mg capsules given once daily for the treatment of a variety of short- and long-term GI conditions. Prilosec is an enteric-coated dosage form for delayed release purpose due to the acid-labile nature of omeprazole.

Santarus previously developed an immediate release (IR) formulation of omeprazole powder for oral suspension (Zegerid) comprised of immediate release omeprazole and sodium bicarbonate, with sodium bicarbonate protecting omeprazole from rapid degradation by gastric acid. In 2004, two dosage strengths of Zegerid IR powder for oral suspension (20 mg under NDA 21-636 and 40 mg under NDA 21-706, respectively) were approved in the US based on 505(b)(2) provision relying on pharmacokinetic (PK) and pharmacodynamic (PD) bridging data to support the reference to the Agency's previous finding of safety and efficacy for Prilosec DR 20 and 40 mg capsules.

The current submission (NDA 21-849) for Zegerid 20 and 40 mg IR capsules, also filed under 505(b)(2) provisions, consists of two clinical pharmacology studies, OME-IR (CAP)-C01 and OME-IR (CAP)-C02, plus supportive studies. Study OME-IR (CAP)-C01 evaluated the PK and PD of omeprazole when Zegerid IR 20 mg capsule was given 1 hour-premeal QD vs. Prilosec DR 20 mg capsule given QD for 7 days. Study OME-IR (CAP)-C02 evaluated similarly the PK and PD of omeprazole when Zegerid IR 40 mg capsule was given 1 hour-premeal QD vs. Prilosec DR 40 mg capsule QD for 7 days. The food effects on Zegerid given 1 hour-postmeal on Day 8 vs. Zegerid given 1 hour-premeal on Day 7 for both Zegerid IR 20 and 40 mg capsules were also investigated.

Based on the Agency's bioequivalence acceptance criteria for PK data obtained from Day 7, Zegerid IR 20 or 40 mg capsule is not bioequivalent (BE) to Prilosec DR 20 or 40 mg capsule, respectively. Zegerid capsules had higher mean C_{max} values than those of Prilosec capsules (17% ↑ for 40 mg dose and 45%↑ for 20 mg dose). However, Zegerid and Prilosec capsules had comparable systemic exposure (AUCs). The higher mean C_{max} value of Zegerid IR 40 mg capsule obtained from this NDA was found to be comparable (3% lower) compared to the mean C_{max} value obtained from Zegerid 40 mg IR powder for oral suspension which has been determined to be safe based on a previous clinical safety study.

Food had significant effects on lowering mean C_{max} (45% ↓) when Zegerid IR 40 mg capsule was given 1 hour-postmeal compared to that given 1 hour-premeal. Food, however, had minor effects on the systemic exposure (AUCs), being 10-15% lower, when Zegerid was given 1 hour-postmeal. Therefore, similar to Zegerid IR powder for oral suspension, Zegerid IR capsules should be given at least 1 hour before a meal.

Comparison of the PD profiles after multiple dosing of Zegerid IR capsules and Prilosec DR capsules indicated that both products are generally similar on all the assessed PD markers for 20 and 40 mg dose levels.

A. Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics (OCPB), NDA 21-849 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. Please see labeling comments (page 11) and Appendix 1 for details. Also, the following dissolution specifications should be conveyed to the sponsor, Q= ——— min for both Zegerid IR 20 and 40 mg capsules.

B. Phase IV Commitments

None

01/03/06

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

Team Leader
Edward D. Bashaw, Pharm. D. _____

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Studies OME-IR (CAP)-C01 and OME-IR (CAP)-C02 are two identical, multiple-dose, BE-type PK/PD studies using a 2 x 2 crossover design with a washout period of at least 10-14 days. In the above PK/PD studies, 1) Zegerid 1 x 20 mg IR capsule (Test) given 1 hour-premeal QD vs. Prilosec 1 x 20 mg DR capsule (Reference) given QD for 7 days and 2) Zegerid 1 x 40 mg IR capsule (Test) given 1 hour-premeal QD vs. Prilosec 1 x 40 mg DR capsule (Reference) given QD for 7 days, respectively, were investigated.

The food effects on Zegerid was also investigated (parallel design), i.e., Zegerid was given 1 hr postmeal on Day 8 compared to those subjects who completed Zegerid IR capsules on Day 7 in Period 1 for both 20 and 40 mg strengths, however, only the results of food study were analyzed and reported for the 40 mg capsule.

Note: For subjects completed Zegerid IR 20 mg capsule given 1 hr premeal during Period 1 (study OME-IR (CAP)-C01), some received Zegerid 20 mg capsule postmeal on Day 9 rather than on Day 8 and some received Zegerid 20 mg capsule on Day 8 postmeal in Period 2. Due to mistake, protocol violation, and insufficient number of subjects completed the Day 8 postmeal study during Period 1, none of the dataset was analyzed for food effects on Zegerid IR 20 mg capsules.

Based on Agency's bioequivalence acceptance criteria on PK data obtained from Day 7, Zegerid IR 20 or 40 mg capsule is not BE to Prilosec DR 20 or 40 mg capsule, respectively. Zegerid capsules had higher mean C_{max} values than those of Prilosec capsules (17% ↑ for 40 mg dose and 45%↑ for 20 mg dose), however, Zegerid and Prilosec capsules had comparable systemic exposure (AUCs). The higher mean C_{max} value of Zegerid IR 40 mg capsule obtained from this NDA was found to be comparable (3% lower) to the mean C_{max} value obtained from Zegerid 40 mg IR powder for oral suspension which has been determined to be safe based on a previous clinical safety study. Food had significant effects on lowering mean C_{max} (45% ↓) of omeprazole when Zegerid IR 40 mg capsule was given 1 hour-postmeal compared to that given 1 hour-premeal. Food had minor effects on the systemic exposure (AUCs), being 10-15% lower, when Zegerid was given 1 hour-postmeal. Therefore, Zegerid IR capsules should be given at least 1 hour before a meal.

For each omeprazole formulation (Reference or Test), the PD data was obtained, 1) % decease from baseline in integrated gastric acidity for the 24-hr interval after the 7th dose on Day 7 (primary), 2) mean gastric concentration, 3) median gastric pH, and 4) % time gastric pH ≤ 4.0.

Comparison of the PD profiles after multiple dosing of Zegerid IR capsules and Prilosec DR capsules indicated that both products are generally similar on all the assessed PD markers for 20 and 40 mg dose levels.

IV. Question Based Review

A. General Attributes:

Omeprazole is a substituted benzimidazole that inhibits gastric acid secretion via specific inhibition of H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Omeprazole has been approved and marketed in the US since 1989 as Prilosec delayed release (DR) capsules 20 and 40 mg for the treatment of a variety of short- and long-term GI conditions. It is enteric-coated for delayed release purpose due to the acid-labile nature of omeprazole. Zegerid (omeprazole) IR powder for oral suspension comprised of immediate release omeprazole and sodium bicarbonate, with sodium bicarbonate protecting omeprazole from rapid degradation by gastric acid.

Santarus' NDAs 21-636 and 21-706 for Zegerid (omeprazole) IR powder for oral suspension 20 and 40 mg, respectively were approved on 06/15/04 and 12/21/04 for the following GI indications: 1) short-term treatment (4-8 weeks) of active duodenal ulcer, 2) short-term treatment (4-8 weeks) of active benign gastric ulcer, 3) heartburn and other symptoms associated with GERD, 4) short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, and 5) maintenance of healing of erosive esophagitis. In addition, with a new clinical trial, a new indication was also approved for the 40 mg oral suspension, i.e., reduction of risk of upper gastrointestinal bleeding in critically ill patients which was not approved before for any of the marketed omeprazole products.

For this NDA (21-849) submitted under 505(b)(2) referencing to NDA 19-810 (Prilosec DR Capsules 20 and 40 mg), the sponsor, Santarus, is seeking approval for another IR dosage form of omeprazole, Zegerid IR 20 and 40 mg capsules. Submitted were two BE–type, PK/PD studies, study Nos. OME-IR (CAP)-C01 and OME-IR-(CAP)-C02, plus two supportive PK/PD studies for oral suspension, study OME-IR (SUSP)-C02 and study OME-IR (SUSP)-C06, which had been reviewed previously.

B. General Clinical Pharmacology:

Q1: Are Zegerid IR 20 and 40 mg capsules BE to Prilosec 20 and 40 mg DR capsules respectively?

A1: Zegerid IR 20 and 40 mg capsules are not BE to their respective Prilosec DR 20 and 40 mg capsules. As expected, Zegerid IR capsules had higher mean C_{max} values

(about 17% ↑ for 40 mg and 45% ↑ for 20 mg doses) as compared to that of Prilosec DR capsules on Day 7. They, however, showed comparable systemic exposure in terms of AUCs.

The higher mean C_{max} value of Zegerid IR 40 mg capsule obtained from this NDA was found to be comparable (3% lower) to the mean C_{max} value obtained from Zegerid 40 mg IR powder for oral suspension which was determined to be safe based on a previous clinical safety study.

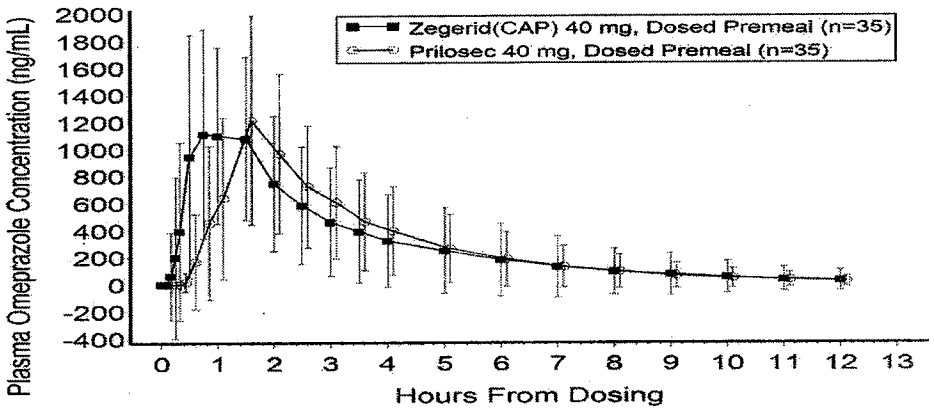
Only the study results obtained from study OME-IR (CAP)-C02 for the 40 mg-dose comparisons are shown in Table 1 and Figure 1:

Table 1. Mean PK Parameters of Omeprazole for Zegerid IR 40 mg Capsule vs. Prilosec DR 40 mg Capsule on Day 7

	Plasma Omeprazole							
	Zegerid(CAP) 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	1526	743.5	35	1344	681.0		
Tmax (hr)	35	0.97	0.61	35	1.51	0.45		
AUC (0-t) (ng*hr/mL)	35	3674	2808	35	3513	2456		
AUC (0-inf) (ng*hr/mL)	35	3806	3112	35	3598	2572		
T½ (hr)	35	1.38	0.76	35	1.51	0.78		
kel (1/hr)	35	0.62	0.26	35	0.56	0.24		
ln (Cmax)	35	7.20	0.53	35	7.05	0.61	116.54	99.05 - 137.11
ln [AUC(0-t)]	35	7.90	0.83	35	7.89	0.79	101.15	92.64 - 110.46
ln [AUC(0-inf)]	**35**	**7.92**	**0.84**	**35**	**7.91**	**0.79**	**101.01**	**92.56 - 110.23**

When given 1 hour-premeal, Zegerid IR 40 mg capsule had higher C_{max} value (about 17% ↑) compared to that of Prilosec DR 40 mg capsule on Day 7. However, Zegerid and Prilosec showed comparable systemic exposure in terms of AUCs on Day 7.

Figure 1. Mean Plasma Profiles of Omeprazole for Zegerid IR 40 mg Capsule vs. Prilosec 40 mg Capsule on Day 7



Complete PK parameters/profiles (and PD parameters) of Zegerid IR capsules and Prilosec DR capsules for 1) comparison on 40 mg dose at Day 1 and 2) comparison on 20 mg dose at both Days 1 and 7 are shown in individual study reports in Appendix 2.

Both C_{max} and AUCs for Zegerid IR 40 mg capsule and Prilosec DR 40 mg capsule increased upon repeated daily dosing. An increase in bioavailability (C_{max} and AUCs) of omeprazole had been reported in the previous NDAs for Zegerid IR powder for oral suspension and for Prilosec DR capsules as well as in the literature which could be due to 1) increase absorption due to increased pH in stomach, 2) auto inhibition of metabolizing enzymes, and 3) decreased clearance of omeprazole.

Q2. Does food (a standardized high fat breakfast) have significant effects on the PK of Zegerid IR capsules?

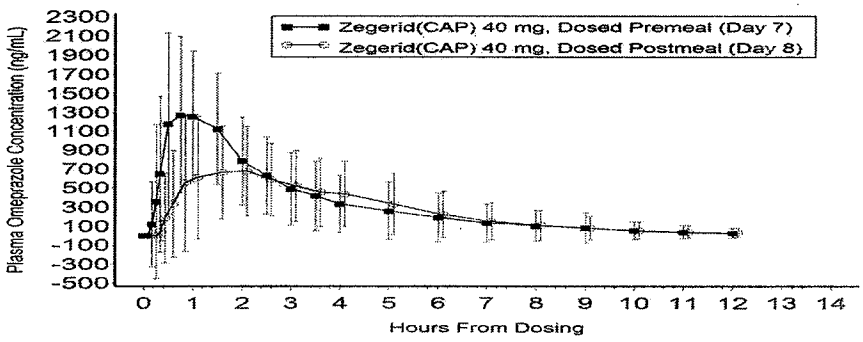
A2. Yes, similar to previously approved Zegerid IR powder for oral suspension, food had significant effects on Zegerid IR 40 mg capsule. When given 1 hour-postmeal (on Day 8), the mean C_{max} of Zegerid was decreased (about 45% ↓) and AUC was decreased (about 22% ↓) compared to that given 1 hour-premeal (on Day 7). Therefore, Zegerid IR capsules should be given at least one hour before a meal.

The food effects on Zegerid IR 40 mg capsules when given 1-hour premeal (Day 7) vs. 1 hour-postmeal (Day 8) are shown below in Table 2 and Figure 2:

Table 2. Zegerid IR 40 mg capsules given 1 hour- postmeal (Day 8) vs. 1-hour premeal (Day 7)

	Plasma Omeprazole							
	Zegerid(CAP) 40 mg (Postmeal)			Zegerid(CAP) 40 mg (Premeal)				
Parameters*	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	18	1026	645.6	18	1646	771.4		
Tmax (hr)	18	1.74	1.27	18	0.93	0.74		
AUC (0-t) (ng*hr/mL)	18	3221	2349	18	3976	2592		
AUC (0-inf) (ng*hr/mL)	18	3321	2488	18	4071	2721		
T½ (hr)	18	1.38	0.66	18	1.38	0.66		
kel (1/hr)	18	0.61	0.26	18	0.61	0.27		
ln (Cmax)	18	6.70	0.79	18	7.28	0.54	55.48	43.07 - 71.45
ln [AUC(0-t)]	18	7.76	0.90	18	8.01	0.84	77.57	70.21 - 85.70
ln [AUC(0-inf)]	18	7.78	0.91	18	8.03	0.85	77.93	70.67 - 85.93

Figure 2. Mean Plasma Profile of Omeprazole When Zegerid given 1 hour-postmeal (Day 8) vs. 1 hour-premeal (Day 7)



Note: This reviewer could not verify/reproduce by either SAS or WinNonlin method for the reported 90% CIs for % Mean Ratio as shown in Table 2, i.e., 43.07 - 71.45 for $\ln(C_{max})$, 70.21 – 85.70 for $\ln(AUC_{0-t})$, and 70.67 – 85.93 for $\ln(AUC_{0-\infty})$ when postmeal (Day 8) and premeal (Day 7) of Zegerid 40 mg capsules were compared. Upon request on 12/06/05, the sponsor submitted on 12/08/05 the detailed analyses including SAS control files used for model, design (parallel), random factors, etc. The 90% CIs determined by this reviewer are as follows below, 37.95 – 81.1 for $\ln(C_{max})$, 47.4 – 126.92 for $\ln(AUC_{0-t})$, and 47.4 – 128.12 for $\ln(AUC_{0-\infty})$. It should also be noted that for systemic exposure (area under the curve), AUC_{0-24} should be used (instead of $AUC_{0-\infty}$). The results of PD analyses are summarized below for 40 mg-dose comparison in Table 3:

Table 3. Mean Comparative PD parameters from Study OME-IR(CAP)-C02

PD Parameters	Zegerid IR 40 mg Capsule	Prilosec DR 40 Capsule
% Decreased from Baseline for Integrated Gastric Acidity (mmol-hr/L)*	Day 1: 45 (range: 5-71) Day 7: 77 (range: 58-94)	Day 1: 56 (range: 28-70) Day 7: 79 (range: 69-98)
Mean Gastric Acid Conc. (mM)	Day 1: 57-64 (range: 23-78) Day 7: 22-29 (range: 1-39)	Day 1: 45-46 (range: 18-66) Day 7: 23-24 (range: 0-37)
Median Gastric pH	Day 1: 2.4-2.8 (range: 1.3-4.9) Day 7: 4.7-5.0 (range: 4.1-5.9)	Day 1: 3.9-4.1 (range: 1.4-5.1) Day 7: 5.0-5.4 (range: 3.9-5.9)
% Time Gastric pH ≤ 4.0	Day 1: 55-62 (range: 35-76) Day 7: 39-42 (range: 16-50)	Day 1: 49-55 (range: 33-76) Day 7: 32-42 (range: 4-49)

*. Claimed as the primary PD endpoint (Day 7) by the sponsor.

The above study showed that on Day 7, Zegerid IR 40 mg capsule and Prilosec DR 40 mg capsule had comparable PD results in terms of % decrease from baseline for integrated gastric acidity, claimed as a primary PD endpoint by the sponsor, (77% vs. 79%). In general, the other PD parameters (as secondary endpoints) also showed comparable results. Similar and comparable PD results were obtained for Zegerid IR 20 mg capsule compared to Prilosec DR 20 mg capsule (e.g., % decrease from baseline for integrated gastric acidity being 72% vs. 70%). Please see individual study reports for detailed PD results (Appendix 2).

Note: On 06/13/05, OCPB sent a request to Division of Scientific Investigation (DSI) through GI Division for an audit for study OME-IR (CAP)-C02 (Zegerid IR 40 mg capsule). At the time of this review, DSI had only completed the audit of the analytical part of the study. An audit of the clinical site in Canada will be conducted at the end of Feb. 06. At the present time, no issues have been identified by DSI that would preclude approval of the application. Once DSI completes the audit at the clinical site and the finalized report becomes available, OCPB will write an addendum to this review documenting those finding and the need for any additional follow-up actions.

C. Intrinsic Factors: None

D. Extrinsic Factors: None

E. General Biopharmaceutics:

Santarus' NDAs 21-636 and 21-706 for Zegerid (omeprazole) IR 20 and 40 mg powder for oral suspension, respectively were the first IR omeprazole formulations approved for indications related to GI disorders and sodium bicarbonate (1,680 mg or 20 meq.) was included in the formulation to protect omeprazole from rapid degradation by gastric acid.

The sponsor further developed omeprazole IR capsules which also included sodium bicarbonate (1,100 mg or 13 meq.). The formulation/compositions of Zegerid 20 and 40 mg capsules are shown below in Table 5:

Table 4. Formulation and Composition of Zegerid IR 20 and 40 mg Capsules

Ingredient	Reference to Quality Standard	Manufacturer	Quantity (20 mg)	Quantity (40 mg)	Function
Omeprazole					
Sodium Bicarbonate			1100 mg	1100 mg	
Croscarmellose Sodium					
Magnesium Stearate					
Gelatin Capsule			1 shell	1 shell	Capsule shell
Total Weight/Unit			**1160 mg**	**1180 mg**	

Both 20 and 40 mg dosage strengths are compositionally identical except for the amounts of omeprazole. The following dissolution methodology was used which is similar to that employed in NDAs for Zegerid IR powder for oral suspension except for paddle speed of 50 rather than 75 rpm (Table 5). The sponsor proposed Q= at 45 min for both strengths.

Table 5. Dissolution Methodology for Zegerid IR 20 and 40 mg Capsules

Apparatus	USP Apparatus 2 (Paddle)
Temperature	37.0 ± 0.5°C
Speed	75 rpm
Volume	900 mL
Dissolution Medium	Phosphate Buffer, pH 7.4
Sampling Volume	5 mL

It should be noted that the original dissolution specification using 50 rpm was picked up based on the stability data at 0, 3, and 6 months. However, the dissolution method using 75 rpm was implemented at 6-month stability data. Therefore, the mean dissolution profiles are only

available at 6 months (the clinically used biobatch and 3 stability batches). As shown below in Table 6 and Figures 3 and 4 are for Zegerid IR 20 and 40 mg capsules used in the PK/PD studies.

Table 6. Mean (CV%) Dissolution Data Obtained from Zegerid 20 and 40 mg biobatches

Capsule Strength	15 min	30 min	45 min	60 min	75 min
20 mg[1]	42 (16%)[2]	86 (11%)	100 (3%)	102 (1%)	103 (1%)
40 mg[1]	71 (3%)	101 (1%)	101 (1%)	99 (1%)	99 (1%)

1. Batches manufactured from clinical trial material (Batch No. 421318 for 20 mg and 421319 for 40 mg).
2. Mean (CV%) dissolution data obtained from 6 capsules.

Figure 3. Mean Dissolution Profile Obtained From The 6-month Stability Data of Zegerid IR 20 mg Capsule

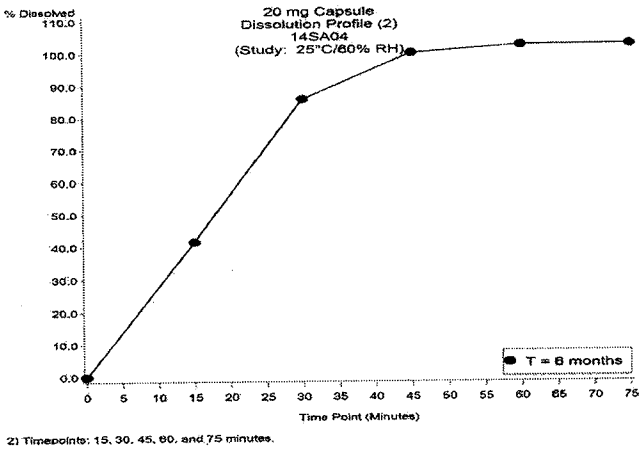
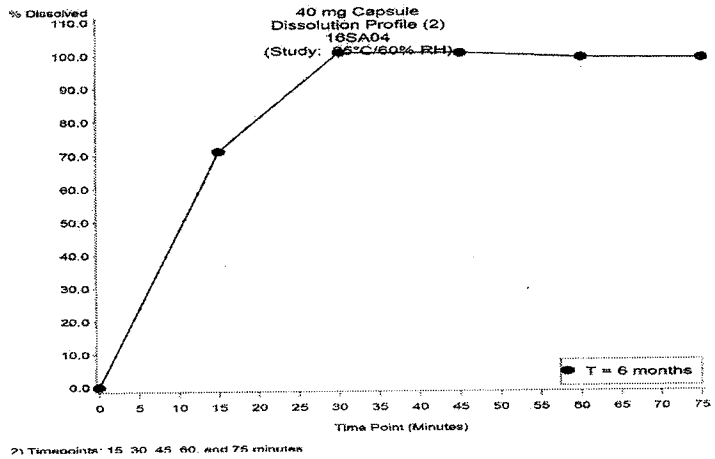


Figure 4. Mean Dissolution Profile Obtained From The 6-month Stability Data of Zegerid IR 40 mg Capsule



The difficulty in setting a dissolution specification for this product lies in limited dissolution data available at 6-month stability testing. Based on the limited dissolution data provided, the following dissolution specifications for both Zegerid IR 20 and 40 mg capsules are recommended: Q= — % at 30 min. Once additional data becomes available, the sponsor may request a data-driven revision to the specification should a large rejection incidence be noted.

F. Analytical Section

An LC-MS/MS method was developed at ———————, and the LLQ was determined to be 5.0 ng/mL. The same assay method was used previously for Zegerid IR powder for oral suspension and it was validated and found acceptable. The summary of the assay results and validation are shown below:

I. **Study OME-IR (Cap)-C01**: Zegerid IR 20 mg capsule

- Standard Curve: 5, 7.5, 10, 25, 50, 100, 200, 500, 600, and 750 ng/mL (n=10)

Accuracy: -0.6% (n=36), 1.6% (n=38), -2.2% (n=38), -0.4% (n=38), 1.0% (n=37), 0.0% (n=37), 1.5% (n=35), -0.4% (n=37), -0.5% (n=38), and 0.4% (n=37)

Precision (CV%): 6.1% (n=36), 4.9% (n=38), 5.1% (n=38), -3.9% (n=38), 3.8% (n=37), 3.6% (n=37), 2.4% (n=35), 3.6% (n=37), 2.4% (n=38), and 2.4% (n=37)

- QC: 15, 100, and 565 ng/mL (n=3)

Accuracy: -4.7% (n=75), -3.9% (n=76), and -3.5% (n=76)
Inter-day variation (CV%): 7.3% (n=75), 6.1% (n=76), and 6.5% (n=76)

II. **Study OME-IR (Cap)-C02**: Zegerid IR 40 mg capsule

- Standard Curve: 5, 7.5, 10, 25, 50, 100, 200, 500, 600, and 750 ng/mL (n=10)

Accuracy: -1.2% (n=36), 1.5% (n=36), -2.8% (n=37), 0.8% (n=36), 1.2% (n=37), 0.0% (n=37), 1.0% (n=37), -0.8% (n=37), 0.5% (n=36), and -0.3% (n=37)

Precision (CV%): 6.0% (n=36), 5.6% (n=36), 4.7% (n=37), 3.7% (n=36), 4.1% (n=37), 3.7% (n=37), 4.3% (n=37), 3.5% (n=37), 2.4% (n=36), and 2.5% (n=37)

- QC: 15, 100, and 565 ng/mL (n=3)

Accuracy: -2.0% (n=97), 1.0% (n=97), and 0.4% (n=96)
Inter-day variation (CV%): 7.6% (n=97), 4.7% (n=97), and 8.3% (n=96)

III. **Assay Method Validation**:

- Standard Curve: 5, 7.5, 10, 25, 50, 100, 200, 500, 600, and 750 ng/mL (n=10)

Accuracy: -3.4% (n=5), 4.0% (n=4), 0.8% (n=5), 3.2% (n=4), 3.4% (n=5), 1.4% (n=4), 2.5% (n=5), -3.4% (n=5), -1.9% (n=5), and -4.9% (n=5)

Precision: Inter-batch variation (CV%)
2.5% (n=5), 2.2% (n=4), 5.7% (n=5), 4.9% (n=4), 4.9% (n=5), 4.2% (n=4), 2.5% (n=5), 4.5% (n=5), 4.2% (n=5), and 3.4% (n=5)

- QC: 15, 100, and 565 ng/mL (n=3)

Inter-batch variation (CV%): 10.5% (n=30), 5.0% (n=30), and 5.1% (n=30)
Intra-batch variation (CV%): 5.9% (n=6), 2.6% (n=6), and 3.2% (n=6)

V. Detailed Labeling Recommendations

1 Page(s) Withheld

____ Trade Secret / Confidential

X Draft Labeling

____ Deliberative Process

VI. Appendices

1. Proposed Package Insert (Original)

2. Individual Study Review

3. Cover Sheet and OCPB Filing/Review Form

NDA 21-849 for Zegerid IR 20 and 40 mg Capsules

Appendix 1

Sponsor's Proposed PI (April, 05 Version)

21 Page(s) Withheld

____ Trade Secret / Confidential

X Draft Labeling

____ Deliberative Process

NDA 21-849 for Zegerid IR 20 and 40 mg Capsules

Appendix 2

Synopses of Individual Study Reviews

2. SYNOPSIS

Name of Sponsor: Santarus, Inc.	*(For National Authority Use Only)*
Name of Finished Product: Zegerid™ (omeprazole) Capsules 20 mg	
Name of Active Ingredient: Omeprazole	
Title of Trial: A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid™ Immediate-Release Capsules 20 mg with Prilosec® Delayed-Release Capsules 20 mg in Healthy Subjects	
Investigator: [redacted] **Trial Center:** [redacted]	
Publication (reference): None	
Date of First Subject Dosed: July 14, 2004 **Date of Last Subject Completed:** August 20, 2004	**Phase of Development:** 1

Trial Objectives:

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

Secondary Objectives: The secondary objectives were as follows:

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

Methodology: This was an open-label, randomized, 2-period crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of 7 consecutive daily doses of Zegerid™ Capsules 20 mg compared to 7 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 to be 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™ Capsules 20 mg or Prilosec 20 mg, as randomized, 1 hour before a standardized high-fat breakfast for 7 consecutive days. Blood samples to determine plasma omeprazole concentrations were collected for 12 hours and gastric pH levels were recorded for 24 hours after the doses on Days 1 and 7. Subjects who had received Zegerid™ 20 mg in Period 1 were to be given an eighth dose (Day 8) 1 hour after the start of the standardized high-fat breakfast. Blood samples were to be 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 there was to be no eighth dose of Zegerid™ 20 mg.

Safety assessments throughout this trial consisted of physical examinations, vital sign measurements, clinical laboratory testing, and monitoring for 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 2 periods, and to ensure that at least 12 of the enrolled subjects completed the eighth treatment day with Zegerid™ Capsules during Period 1. Thirty-six subjects were dosed and 30 subjects completed 7 days of dosing in each period of the trial. Thirty subjects were included in the pharmacokinetic analysis and 25 subjects were included in the pharmacodynamic analysis for Doses 1 and 7. Because of an error in postmeal administration of Zegerid™ on Day 8 (Period 1), pharmacokinetic analyses for postmeal administration of Zegerid™ Capsules 20 mg were not completed.
Diagnosis and Main Criteria for Inclusion and Exclusion: Participants in this trial were healthy non-Asian subjects (males and nonlactating, nonpregnant females), 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 Product, Dose and Mode of Administration, Batch Number: Zegerid™ Capsules 20 mg (Lot 421471) were to be administered orally with 120 mL (4 oz) water once daily for 8 consecutive days in half of the subjects and once daily for 7 consecutive days in the other half.
Duration of Treatment: Including screening, subjects participated in this trial for up to 40 days.
Reference Product, 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™ Capsules 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
- Percent time 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™ Capsules 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™ to 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 2 treatment periods using an ANOVA model. If there were no statistically significant differences in baseline values for integrated gastric acidity, the baseline values for the 2 periods were averaged when calculating change from Baseline; otherwise, the corresponding baseline value for that period was 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™ Capsules 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™ to Prilosec, were between 80% and 125%.

Summary of Results:

Safety Results: There were no deaths, SAEs, or other significant AEs during this trial. The number of subjects with AEs during the Zegerid-treatment period was similar to the number of subjects with AEs during the Prilosec-treatment period. 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™ Capsules 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™ (CAP) 20 mg and Prilosec 20 mg Administered Premeal

	Plasma Omeprazole							
	Zegerid(CAP) 20 mg			Prilosec 20 mg				
Parameters*	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	30	679.8	299.2	30	487.4	256.8		
Tmax (hr)	30	0.82	0.43	30	1.30	0.51		
AUC (0-t) (ng•hr/mL)	30	1021	691.2	30	898.3	595.9		
AUC (0-inf) (ng•hr/mL)	30	1031	694.4	30	909.5	597.6		
T½ (hr)	30	0.95	0.36	30	1.03	0.35		
kel (1/hr)	30	0.83	0.29	30	0.75	0.25		
ln (Cmax)	30	6.43	0.44	30	6.08	0.53	145.46	123.56 - 171.25
ln [AUC(0-t)]	30	6.74	0.61	30	6.61	0.61	113.79	105.34 - 122.92
ln [AUC(0-inf)]	30	6.75	0.60	30	6.63	0.60	113.30	105.02 - 122.22

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.

The primary pharmacokinetic analysis was based on ln[AUC(0-inf)] on Day 7.

The primary pharmacokinetic endpoint was AUC(0-inf) at steady state (Day 7). Table I illustrates that Zegerid™ Capsules 20 mg and Prilosec 20 mg administered once daily before breakfast, were bioequivalent with respect to AUC(0-inf). The percent mean ratio was 113.30%, and the bounds of the 90% CI were 105.02% and 122.22%. The Cmax for Zegerid™ 20 mg at steady state was greater than for Prilosec 20 mg (percent mean ratio of 145.46%, 90% CI of 123.56% to 171.25%). The Tmax was significantly shorter for Zegerid™ 20 mg than for Prilosec 20 mg ($p<0.001$).

During the conduct of the OME-IR(CAP)-C01 clinical trial, the contract research organization responsible for execution of the trial failed to properly complete activities related to Dose 8 (postmeal administration of Zegerid™ 20-mg capsules) as directed by the original protocol. Because of this protocol violation, insufficient data were provided to assess the effect of food on the pharmacokinetics of Zegerid™ 20-mg capsules.

Pharmacodynamic Results:

Table II. Assessment of Pharmacodynamic Equivalence Between Zegerid™ (CAP) 20 mg and Prilosec 20 mg

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity	Zegerid(CAP) 20 mg			Prilosec 20 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio**	90% CI**
Day 7	25	70.87	15.58	25	69.19	14.09	102.12	95.65 – 109.03

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.

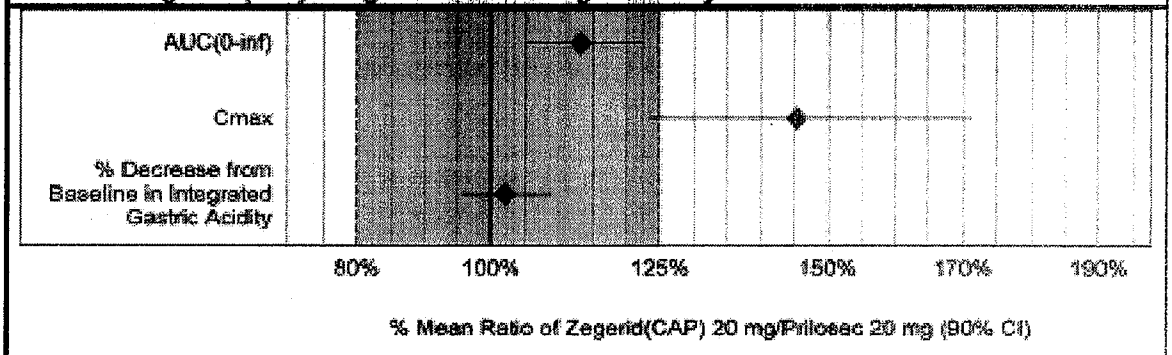
** An ANOVA model was used to test the pharmacodynamic equivalence of Zegerid™ Capsules and Prilosec, using the natural logarithmic transformation of percent decrease from Baseline in integrated gastric acidity. The model included the following factors: treatment, period, sequence, and subject nested 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 of Zegerid™ to Prilosec were between 80% and 125%.

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

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

Conclusion: Zegerid™ Capsules 20 mg were equivalent to Prilosec Capsules 20 mg with regard to AUC(0-inf) and percent decrease from Baseline in integrated gastric acidity on Day 7 (Figure I). The 2 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™ Capsules 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™ (CAP) 20 mg and Prilosec 20 mg After 7 Days



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

Both Zegerid™ Capsules 20 mg and Prilosec Capsules 20 mg were well tolerated during the 7-day to 9-day (Zegerid™ Capsules, 8 doses over 9 days) dosing periods in this trial. No meaningful differences between the treatments were observed with respect to safety.

Date of the Report: **February 14, 2005**

Study Results:

I. PK Data:

Table 1. Mean PK Parameters of Omeprazole for Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule on Day 1

	Plasma Omeprazole							
	Zegerid(CAP) 20 mg			Prilosec 20 mg				
		Arithmetic			Arithmetic		% Mean	90% CI for
Parameters*	n	Mean	SD	n	Mean	SD	Ratio	% Mean Ratio
Cmax (ng/mL)	30	498.1	253.4	30	328.0	158.4		
Tmax (hr)	30	0.61	0.30	30	1.41	0.39		
AUC (0-t) (ng*hr/mL)	30	501.8	307.1	30	467.0	267.4		
AUC (0-inf) (ng*hr/mL)	30	509.7	308.4	30	475.6	268.6		
T½ (hr)	30	0.75	0.47	30	0.79	0.33		
kel (1/hr)	30	1.09	0.34	30	0.99	0.31		
ln (Cmax)	30	6.08	0.54	30	5.68	0.48	148.49	129.16 - 170.72
ln [AUC(0-t)]	30	6.06	0.56	30	6.01	0.53	105.48	98.92 - 112.47
ln [AUC(0-inf)]	30	6.08	0.55	30	6.03	0.52	105.31	98.94 - 112.09

Figure 1. Mean Plasma Omeprazole Profiles of Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule on Day 1

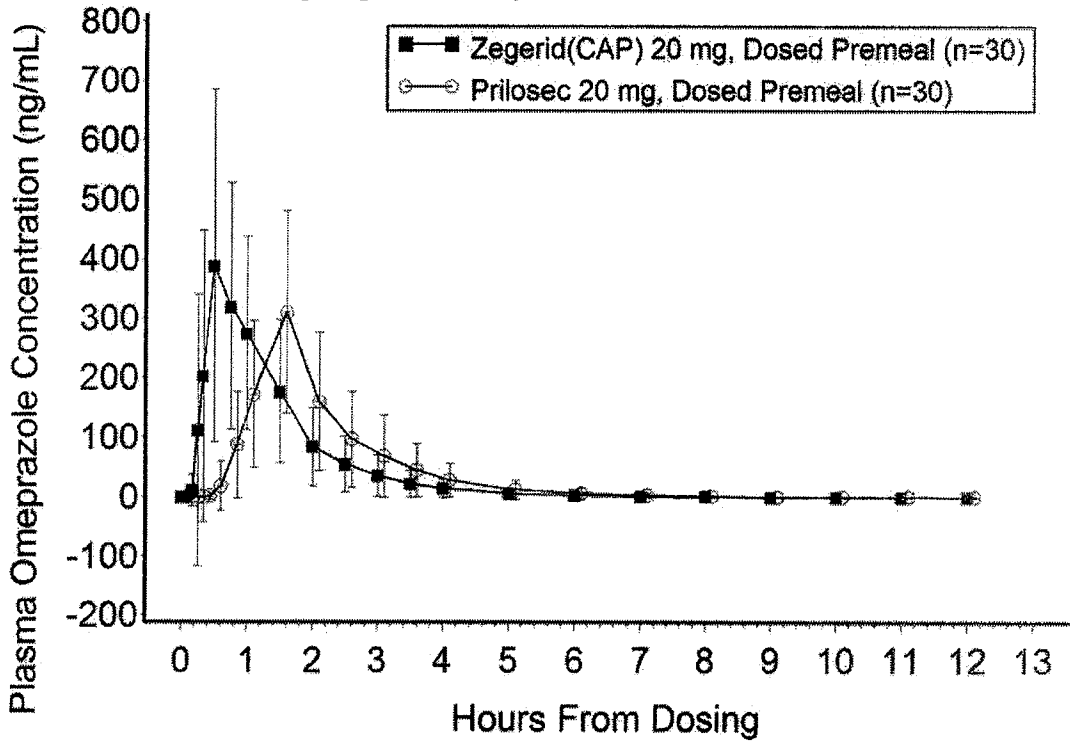
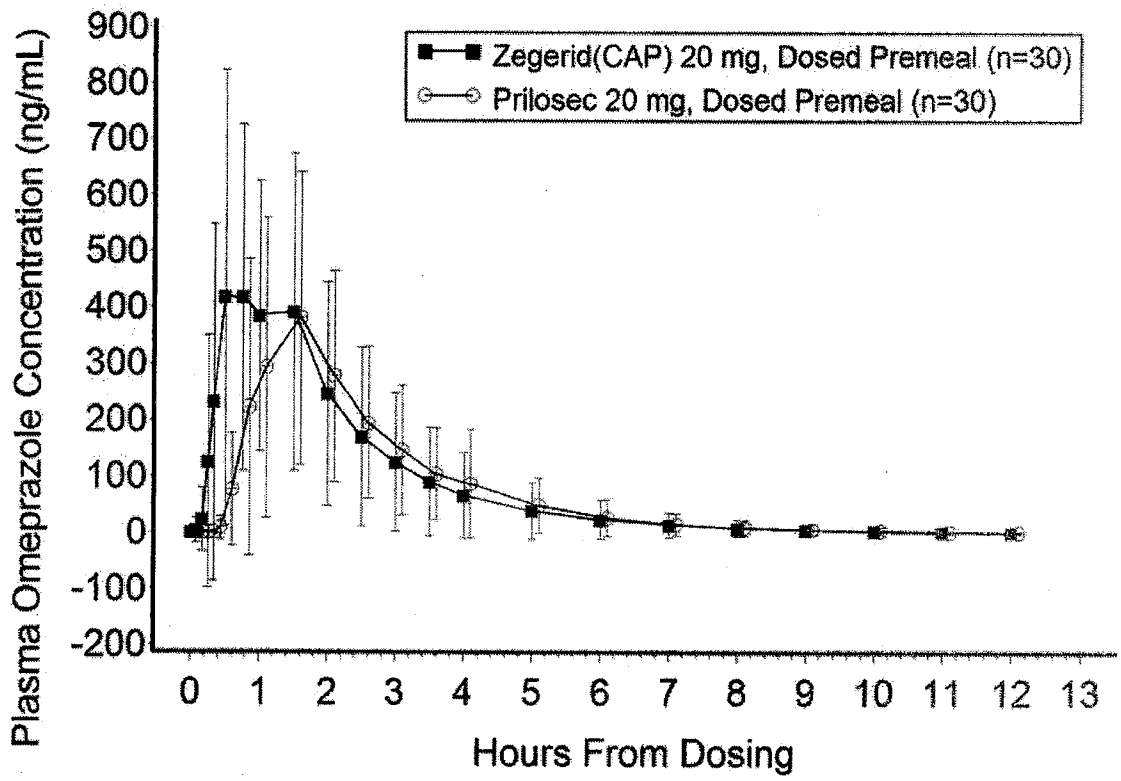


Table 2. Mean PK Parameters of Omeprazole for Zegerid IR 20 mg Capsule and Prilosec 20 mg Capsule on Day 7

	Plasma Omeprazole							
	Zegerid(CAP) 20 mg			Prilosec 20 mg				
		Arithmetic			Arithmetic		% Mean	90% CI for
Parameters*	n	Mean	SD	n	Mean	SD	Ratio	% Mean Ratio
Cmax (ng/mL)	30	679.8	299.2	30	487.4	256.8		
Tmax (hr)	30	0.82	0.43	30	1.30	0.51		
AUC (0-t) (ng*hr/mL)	30	1021	691.2	30	898.3	595.9		
AUC (0-inf) (ng*hr/mL)	30	1031	694.4	30	909.5	597.6		
T½ (hr)	30	0.95	0.36	30	1.03	0.35		
kel (1/hr)	30	0.83	0.29	30	0.75	0.25		
ln (Cmax)	30	6.43	0.44	30	6.06	0.53	145.46	123.56 - 171.25
ln [AUC(0-t)]	30	6.74	0.61	30	6.61	0.61	113.79	105.34 - 122.92
ln [AUC(0-inf)]	**30**	**6.75**	**0.60**	**30**	**6.63**	**0.60**	**113.30**	**105.02 - 122.22**

Figure 2. Mean Plasma Omeprazole Profiles of Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule on Day 7



Note: No food effect study was done.

II. PD Data:

Table 3. Cumulative Integrated Gastric Acidity with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule

Assessment	Cumulative Integrated Gastric Acidity (mmol•hr/L) Zegerid(CAP) 20 mg	Prilosec 20 mg	Zegerid(CAP)/Prilosec (%) By-Subject Ratios
Baseline	2733 (2065 - 3115)	2854 (2159 - 2994)	101 (78 - 117)
Day 1	2084 (1773 - 2782)	1967 (1323 - 2273)	118 (98 - 133)
Day 7	812 (542 - 1074)	826 (618 - 920)	99 (73 - 116)
Percent Decrease from Baseline* to:			
Day 1	18 (-9 - 41)	28 (15 - 44)	73 (12 - 110)
Day 7	72 (58 - 80)	70 (62 - 77)	104 (95 - 110)

Figure 3. Cumulative Integrated Gastric Acidity with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

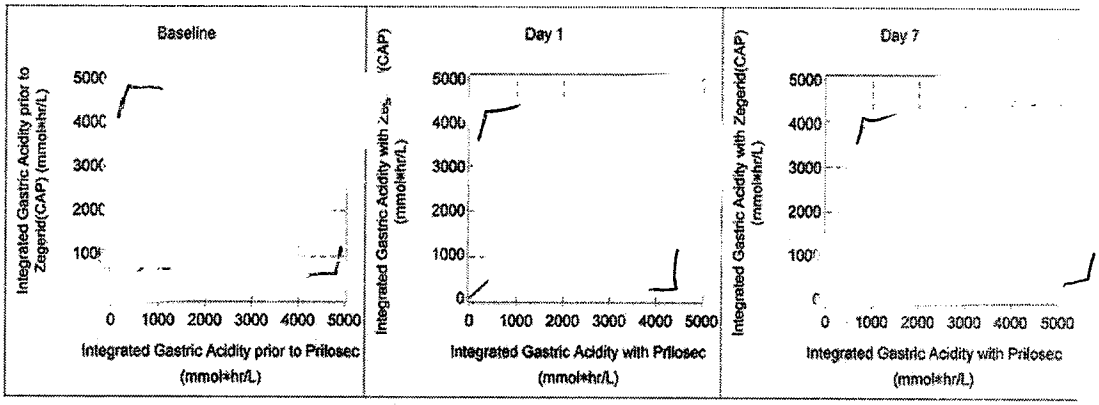


Figure 4. Cumulative Integrated Gastric Acidity with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7

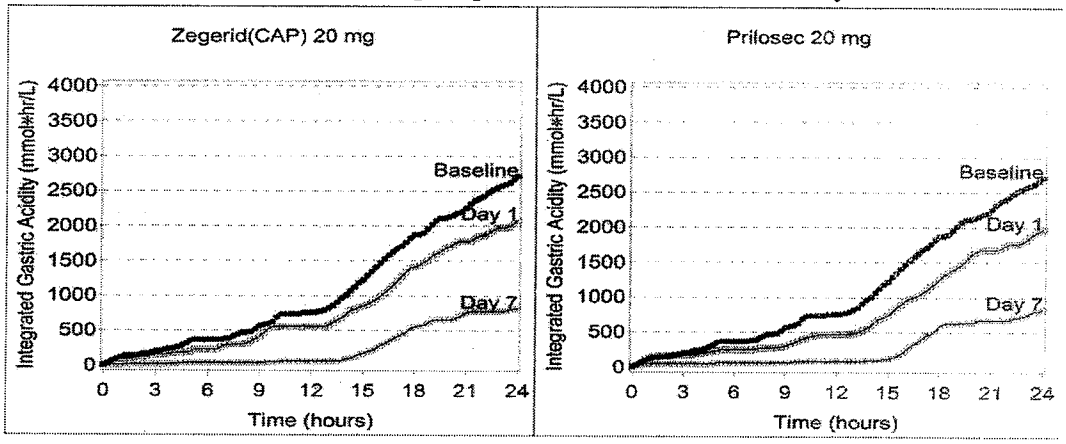


Table 4. Mean Gastric Acid Concentration with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule

Assessment	Mean Gastric Acid Concentration (mM) Zegerid(CAP) 20 mg	Prilosec 20 mg	Zegerid(CAP)/Prilosec (%) By-Subject Ratios
Baseline	114 (86 - 130)	119 (90 - 125)	101 (78 - 117)
Day 1	87 (74 - 116)	82 (55 - 95)	118 (98 - 133)
Day 7	34 (23 - 45)	34 (26 - 38)	89 (73 - 116)
Percent Decrease from Baseline* to:			
Day 1	18 (-9 - 41)	28 (15 - 44)	73 (12 - 110)
Day 7	72 (58 - 80)	70 (62 - 77)	104 (96 - 110)

Figure 5. Mean Gastric Acid Concentration with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

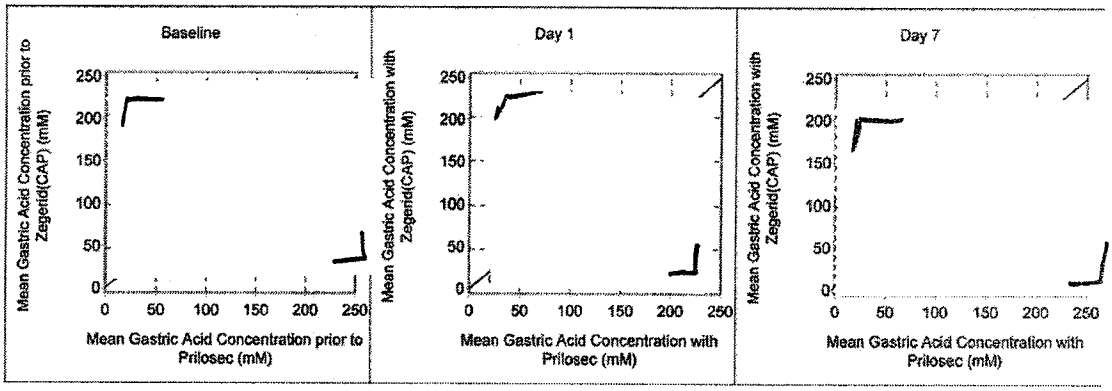


Figure 6. Mean Gastric Acid Concentration with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7

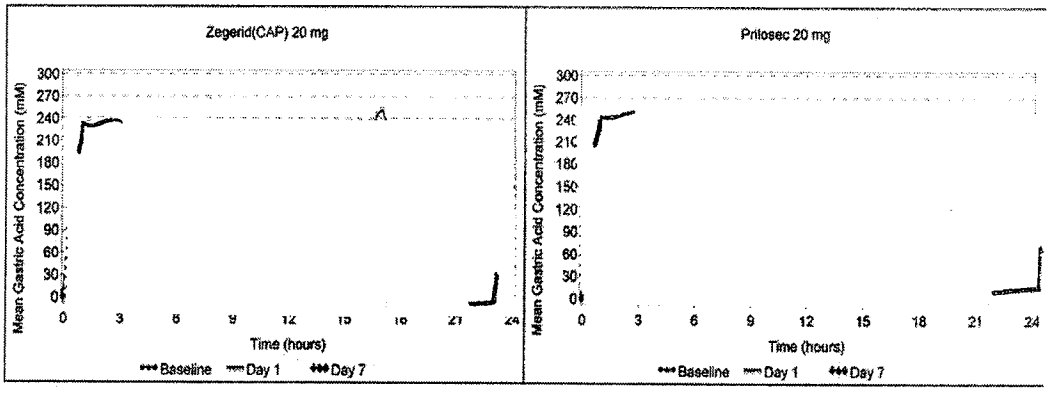


Table 5. Median Gastric pH with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule

Assessment	Median Gastric pH		
	Zegerid(CAP) 20 mg	Prilosec 20 mg	Zegerid(CAP)/Prilosec (%) By-Subject Ratios
Baseline	0.92 (0.83 - 1.18)	1.02 (0.85 - 1.19)	93 (84 - 104)
Day 1	1.31 (0.96 - 2.06)	1.37 (1.08 - 2.56)	100 (75 - 127)
Day 7	4.46 (3.83 - 5.52)	4.49 (3.89 - 5.45)	100 (82 - 108)
Increase from Baseline* to:			
Day 1	0.32 (0.03 - 0.74)	0.33 (0.16 - 1.09)	52 (-1 - 141)
Day 7	3.39 (2.44 - 4.12)	3.48 (3.02 - 4.15)	100 (79 - 110)

Figure 7. Median Gastric pH with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

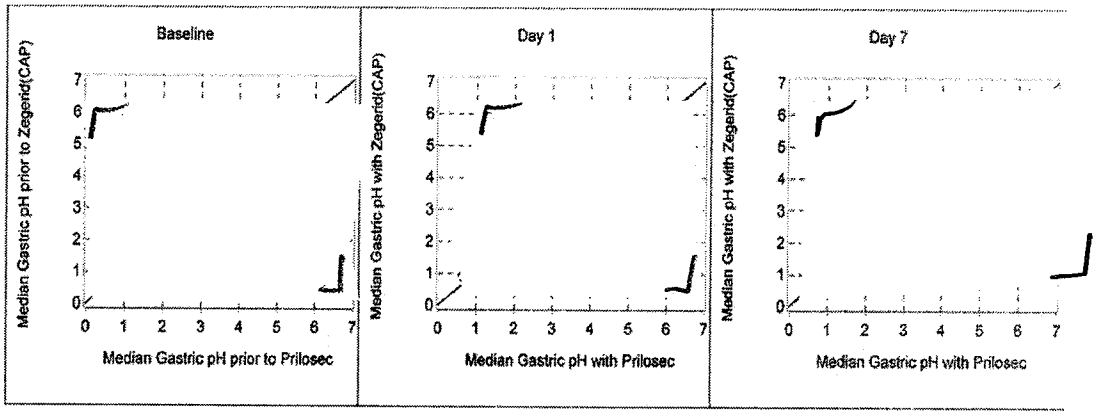


Figure 8. Median Gastric Acid Concentration with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule on Days 1 and 7

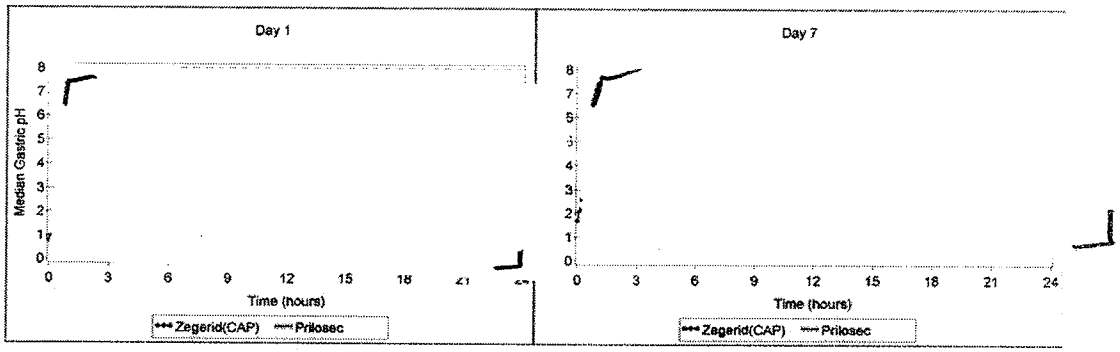


Table 6. Percent Time Gastric pH ≤ 4 with Zegerid IR 20 mg Capsule 20 mg and Prilosec DR 20 mg Capsule

Assessment	Percent Time Gastric pH ≤ 4		
	Zegerid(CAP) 20 mg	Prilosec 20 mg	Zegerid(CAP)/Prilosec (%) By-Subject Ratios
Baseline	86 (81 - 92)	85 (78 - 91)	101 (96 - 110)
Day 1	78 (71 - 89)	76 (64 - 86)	101 (89 - 116)
Day 7	43 (33 - 54)	46 (36 - 52)	108 (83 - 119)
Percent Decrease from Baseline* to:			
Day 1	5 (0 - 17)	6 (2 - 19)	79 (13 - 232)
Day 7	47 (37 - 60)	46 (40 - 55)	96 (78 - 113)

Figure 9. Percent Time Gastric pH ≤ 4 with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

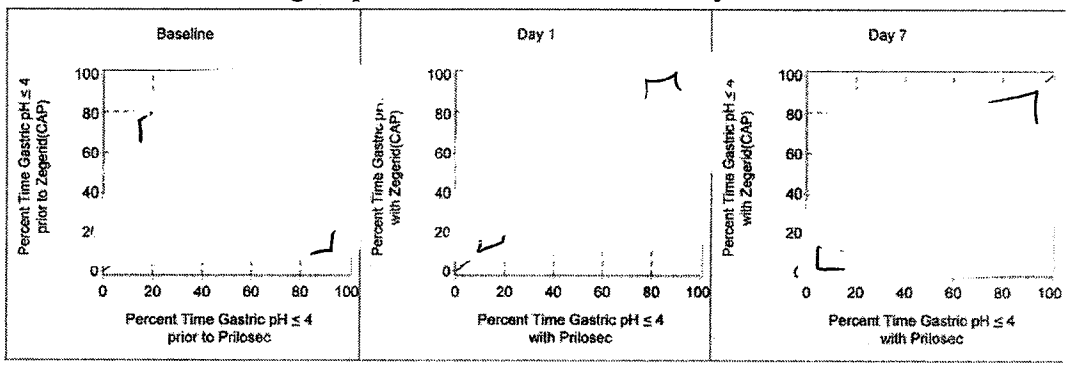
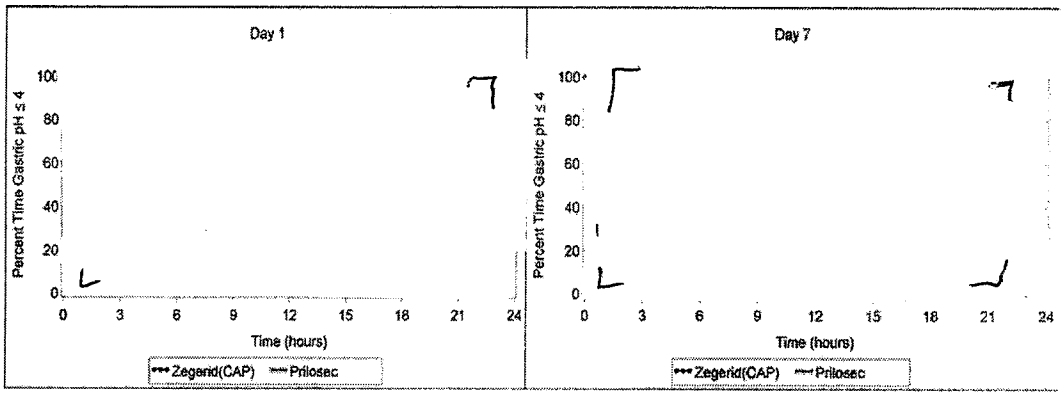


Figure 10. Percent Time Gastric pH ≤ 4 with Zegerid IR 20 mg Capsule and Prilosec DR 20 mg Capsule on Days 1 and 7



2. SYNOPSIS

Name of Sponsor: Santarus, Inc.	*(For National Authority Use Only)*
Name of Finished Product: Zegerid™ (omeprazole) Capsules 40 mg	
Name of Active Ingredient: Omeprazole	
Title of Trial: A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid™ Immediate-Release Capsules 40 mg with Prilosec® Delayed-Release Capsules 40 mg in Healthy Subjects	
Investigator: [redacted] **Trial Center:** [redacted]	
Publication (reference): None	
Date of First Subject Enrolled: August 23, 2004 **Date of Last Subject Completed:** September 29, 2004	**Phase of Development:** 1

Trial Objectives:

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

Secondary Objectives: The secondary objectives were as follows:

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

Methodology: This was an open-label, randomized, 2-period crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of 7 consecutive daily doses of Zegerid™ Capsules 40 mg compared to 7 consecutive 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™ Capsules 40 mg or Prilosec 40 mg, as randomized, 1 hour before a standardized high-fat breakfast for 7 consecutive days. Blood samples to determine plasma omeprazole concentrations were collected for 12 hours and gastric pH levels were recorded for 24 hours after the doses on Days 1 and 7. Subjects who had received Zegerid™ 40 mg in Period 1 were given an eighth dose (Day 8) 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 there was no eighth dose of Zegerid™ 40 mg.

Safety assessments throughout this trial consisted of physical examinations, vital sign measurements, clinical laboratory testing, and monitoring for 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 2 periods, and to ensure that at least 12 of the enrolled subjects completed the eighth treatment day with Zegerid™ Capsules 40 mg during Period 1. Thirty-six subjects were dosed and 35 subjects completed the trial. Thirty-five subjects were included in the pharmacokinetic analysis and 34 subjects were included in the pharmacodynamic analysis for Doses 1 and 7. Eighteen 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 subjects (males and nonlactating, nonpregnant females), 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 Product, Dose and Mode of Administration, Batch Number: Zegerid™ Capsules 40 mg (Lot 421473) were administered orally with 120 mL (4 oz) water once daily for 8 consecutive days in half of the subjects and once daily for 7 consecutive days in the other half.
Duration of Treatment: Including screening, subjects participated in this trial for up to 41 days.
Reference Product, Dose, and Mode of Administration, Batch Number: Prilosec® 40 mg (omeprazole, manufactured for AstraZeneca, Inc., by Merck & Co., Inc., Lot 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™ Capsules 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
- Percent time 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™ Capsules 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™ to 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 2 treatment periods using an ANOVA model. If there were no statistically significant differences in baseline values for integrated gastric acidity, the baseline values for the 2 periods were averaged when calculating change from Baseline; otherwise, the corresponding baseline value for that period was 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™ Capsules 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™ to Prilosec, were between 80% and 125%.

Summary of Results:

Safety Results: There were no deaths, SAEs, or other significant AEs during this trial. The number of subjects with AEs during the Zegerid-treatment period was similar to the number of subjects with AEs during the Prilosec-treatment period. 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™ Capsules 40 mg and Prilosec 40 mg, administered premeal at steady state (Day 7), are presented in Table 1.

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

	Plasma Omeprazole							
	Zegerid(CAP) 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	1526	743.5	35	1344	681.0		
Tmax (hr)	35	0.97	0.61	35	1.51	0.45		
AUC (0-t) (ng•hr/mL)	35	3674	2808	35	3513	2456		
AUC (0-inf) (ng•hr/mL)	35	3808	3112	35	3598	2572		
T½ (hr)	35	1.38	0.76	35	1.51	0.78		
kel (1/hr)	35	0.62	0.26	35	0.56	0.24		
ln (Cmax)	35	7.20	0.53	35	7.05	0.61	116.54	99.05 - 137.11
ln [AUC(0-t)]	35	7.90	0.83	35	7.89	0.79	101.15	92.64 - 110.46
ln [AUC(0-inf)]	**35**	**7.92**	**0.84**	**35**	**7.91**	**0.79**	**101.01**	92.56 - 110.23

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.
The primary pharmacokinetic analysis was based on ln[AUC(0-inf)] on Day 7.

The primary pharmacokinetic endpoint was AUC(0-inf) at steady state (Day 7). Table I illustrates that Zegerid™ Capsules 40 mg and Prilosec 40 mg administered once daily before breakfast, were bioequivalent with respect to AUC(0-inf). The percent mean ratio was 101.01%, and the bounds of the 90% CI were 92.56% and 110.23%. The Cmax for Zegerid™ 40 mg at steady state was greater than for Prilosec 40 mg (percent mean ratio of 116.54%, 90% CI of 99.05% to 137.11%). 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™ (CAP) 40 mg Administered Postmeal vs. Premeal

	Plasma Omeprazole							
	Zegerid(CAP) 40 mg (Postmeal)			Zegerid(CAP) 40 mg (Premeal)				
Parameters*	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	18	1026	645.6	18	1646	771.4		
Tmax (hr)	18	1.74	1.27	18	0.93	0.74		
AUC (0-t) (ng•hr/mL)	18	3221	2349	18	3976	2592		
AUC (0-inf) (ng•hr/mL)	18	3321	2488	18	4071	2721		
T½ (hr)	18	1.38	0.66	18	1.38	0.66		
kel (1/hr)	18	0.61	0.26	18	0.61	0.27		
ln (Cmax)	18	6.70	0.79	18	7.28	0.54	55.48	43.07 - 71.45
ln [AUC(0-t)]	18	7.76	0.90	18	8.01	0.84	77.57	70.21 - 85.70
ln [AUC(0-inf)]	18	7.78	0.91	18	8.03	0.85	77.93	70.67 - 85.93

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 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.

Total bioavailability of Zegerid™ Capsules 40 mg, AUC(0-inf), was decreased by 22% when Zegerid™ was administered 1 hour after the beginning of a meal (Table II). Administration of Zegerid™ Capsules 40 mg after the meal lowered the Cmax mean ratio by 45% (postmeal:premeal) and delayed the mean Tmax by 0.81 hours (49 minutes).

Pharmacodynamic Results:

Table III. **Assessment of Pharmacodynamic Equivalence Between Zegerid™ (CAP) 40 mg and Prilosec 40 mg**

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity	Zegerid(CAP) 40 mg			Prilosec 40 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio**	90% CI**
Day 7	34	73.51	22.99	34	79.64	16.95	88.51	80.06 – 97.86

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

* When calculating the percent decrease from Baseline, the corresponding value for that period was used.

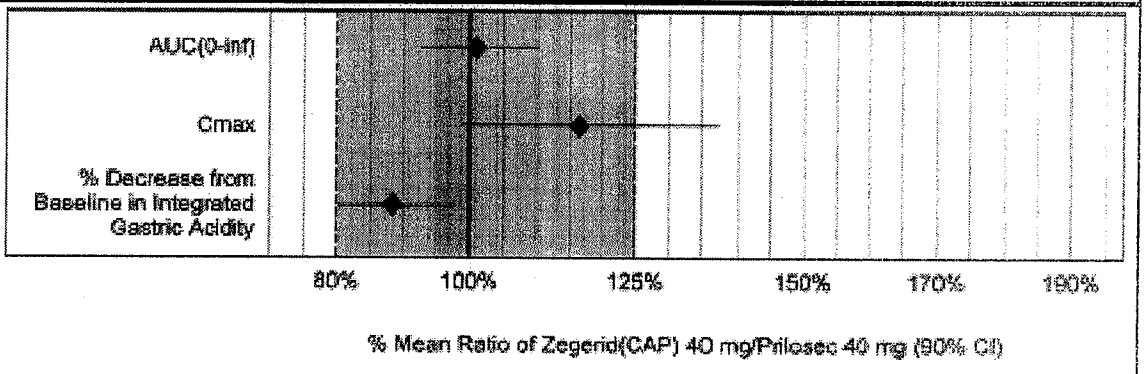
** An ANOVA model was used to test the pharmacodynamic equivalence of Zegerid™ Capsules and Prilosec, using the natural logarithmic transformation of percent decrease from Baseline in integrated gastric acidity. The model included the following factors: treatment, period, sequence, and subject nested 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 of Zegerid™ to Prilosec were between 80% and 125%.

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

Zegerid™ Capsules 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™ Capsules 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 2 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™ Capsules 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™ (CAP) 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 22% decrease in bioavailability of omeprazole in the presence of food when Zegerid™ was dosed following a standardized high-fat breakfast on Day 8. The bioavailability [AUC(0-inf)] of omeprazole from Zegerid™ 40 mg postmeal on Day 8, however, was greater than the bioavailability [AUC(0-inf)] of omeprazole from Zegerid™ 40 mg or from Prilosec 40 mg premeal on Day 1.

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

Date of the Report: **February 14, 2005**

Appears This Way
On Original

Study Results:

I. PK Data:

Table 1. Mean PK Parameters of Omeprazole for Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule on Day 1

	Plasma Omeprazole							
	Zegerid(CAP) 40 mg			Prilosec 40 mg				
	Arithmetic			Arithmetic			% Mean	90% CI for
Parameters*	n	Mean	SD	n	Mean	SD	Ratio	% Mean Ratio
Cmax (ng/mL)	35	1154	611.9	35	887.5	694.0		
Tmax (hr)	35	0.56	0.26	35	1.51	0.40		
AUC (0-t) (ng*hr/mL)	35	1841	2145	35	1767	2016		
AUC (0-inf) (ng*hr/mL)	35	1882	2263	35	1843	2092		
T½ (hr)	35	0.92	0.61	35	2.26	6.37		
kel (1/hr)	35	0.98	0.39	35	0.74	0.39		
ln (Cmax)	35	6.91	0.56	35	6.51	0.78	149.23	125.53 - 177.40
ln [AUC(0-t)]	35	7.06	0.92	35	6.98	0.98	107.98	99.48 - 117.21
ln [AUC(0-inf)]	35	7.07	0.93	35	7.06	0.93	101.41	92.68 - 110.96

Figure 1. Mean Plasma Profiles of Omeprazole for Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule on Day 1

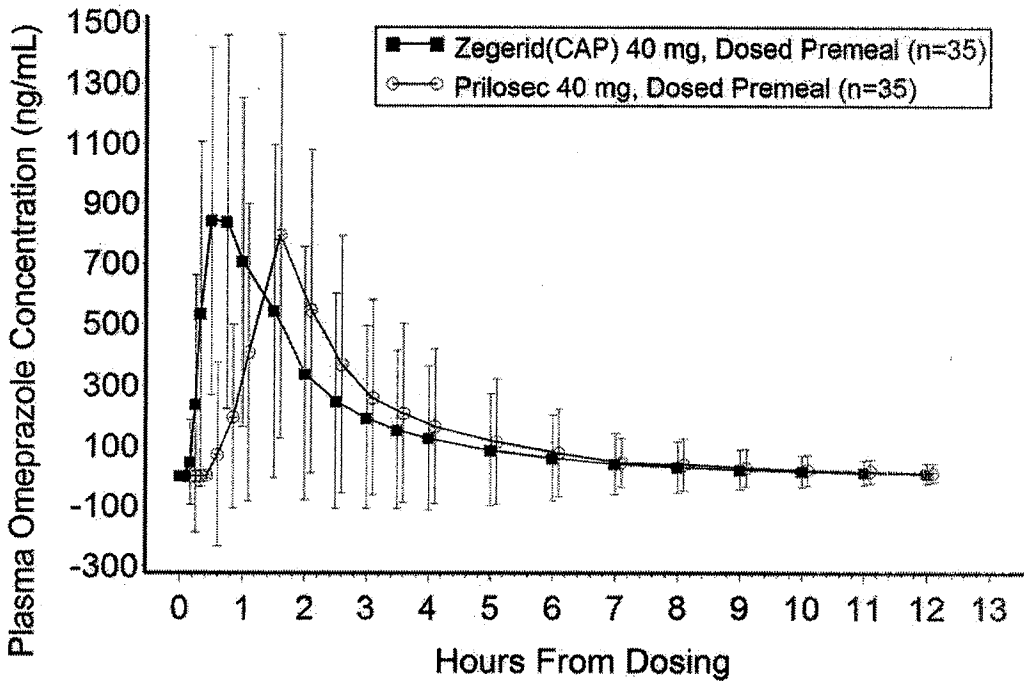


Table 2. **Mean PK Parameters of Omeprazole for Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule on Day 7**

	Plasma Omeprazole							
	Zegerid(CAP) 40 mg			Prilosec 40 mg				
		Arithmetic			Arithmetic		% Mean	90% CI for
Parameters*	n	Mean	SD	n	Mean	SD	Ratio	% Mean Ratio
Cmax (ng/mL)	35	1526	743.5	35	1344	681.0		
Tmax (hr)	35	0.97	0.61	35	1.51	0.45		
AUC (0-t) (ng*hr/mL)	35	3674	2808	35	3513	2456		
AUC (0-inf) (ng*hr/mL)	35	3806	3112	35	3598	2572		
T½ (hr)	35	1.38	0.76	35	1.51	0.78		
kel (1/hr)	35	0.62	0.26	35	0.56	0.24		
ln (Cmax)	35	7.20	0.53	35	7.05	0.61	116.54	99.05 - 137.11
ln [AUC(0-t)]	35	7.90	0.83	35	7.89	0.79	101.15	92.64 - 110.46
ln [AUC(0-inf)]	**35**	**7.92**	**0.84**	**35**	**7.91**	**0.79**	**101.01**	**92.56 - 110.23**

Figure 2. **Mean Plasma Profiles of Omeprazole for Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule on Day 7**

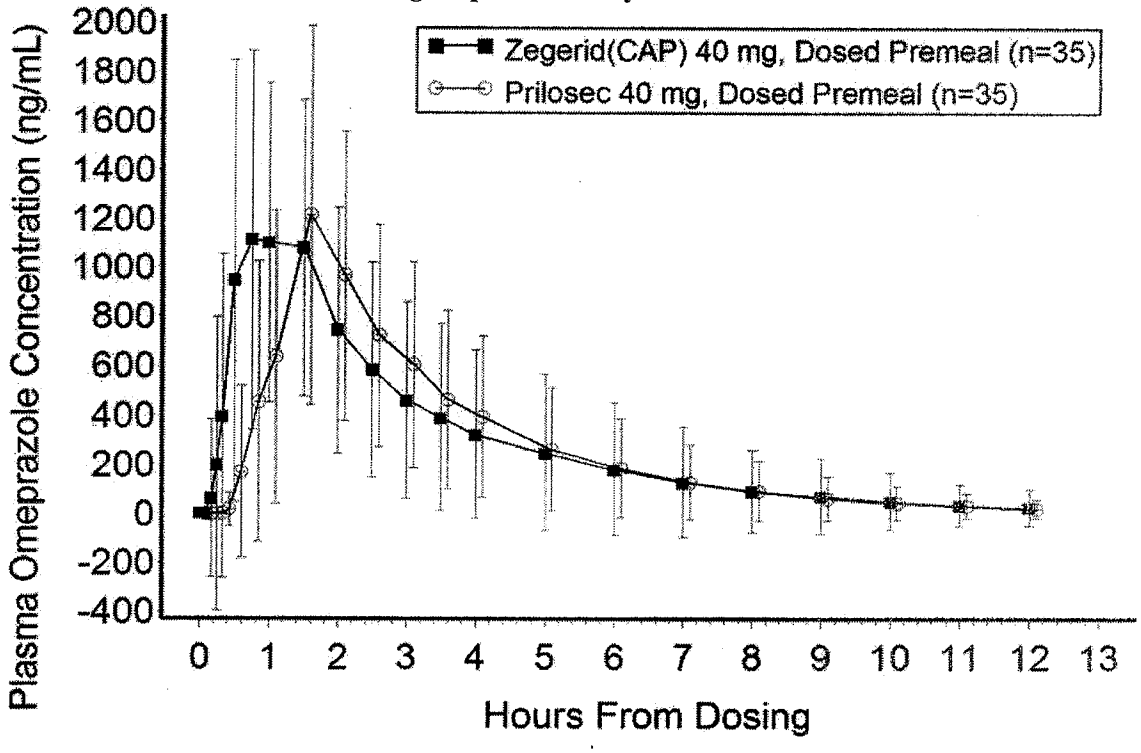


Table 3. **Zegerid IR 40 mg capsules given 1 hour- postmeal (Day 8) and 1-hour premeal (Day 7)**

	Plasma Omeprazole							
	Zegerid(CAP) 40 mg (Postmeal)			Zegerid(CAP) 40 mg (Premeal)				
Parameters*	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	18	1026	645.6	18	1646	771.4		
Tmax (hr)	18	1.74	1.27	18	0.93	0.74		
AUC (0-t) (ng*hr/mL)	18	3221	2349	18	3976	2592		
AUC (0-inf) (ng*hr/mL)	18	3321	2488	18	4071	2721		
T½ (hr)	18	1.38	0.66	18	1.38	0.66		
kel (1/hr)	18	0.61	0.26	18	0.61	0.27		
ln (Cmax)	18	6.70	0.79	18	7.28	0.54	55.48	43.07 - 71.45
ln [AUC(0-t)]	18	7.76	0.90	18	8.01	0.84	77.57	70.21 - 85.70
ln [AUC(0-inf)]	18	7.78	0.91	18	8.03	0.85	77.93	70.67 - 85.93

Figure 3. **Mean Plasma Profile of Omeprazole When Zegerid Given 1 hour-postmeal (Day 8) and 1 hour-premeal (Day 7)**

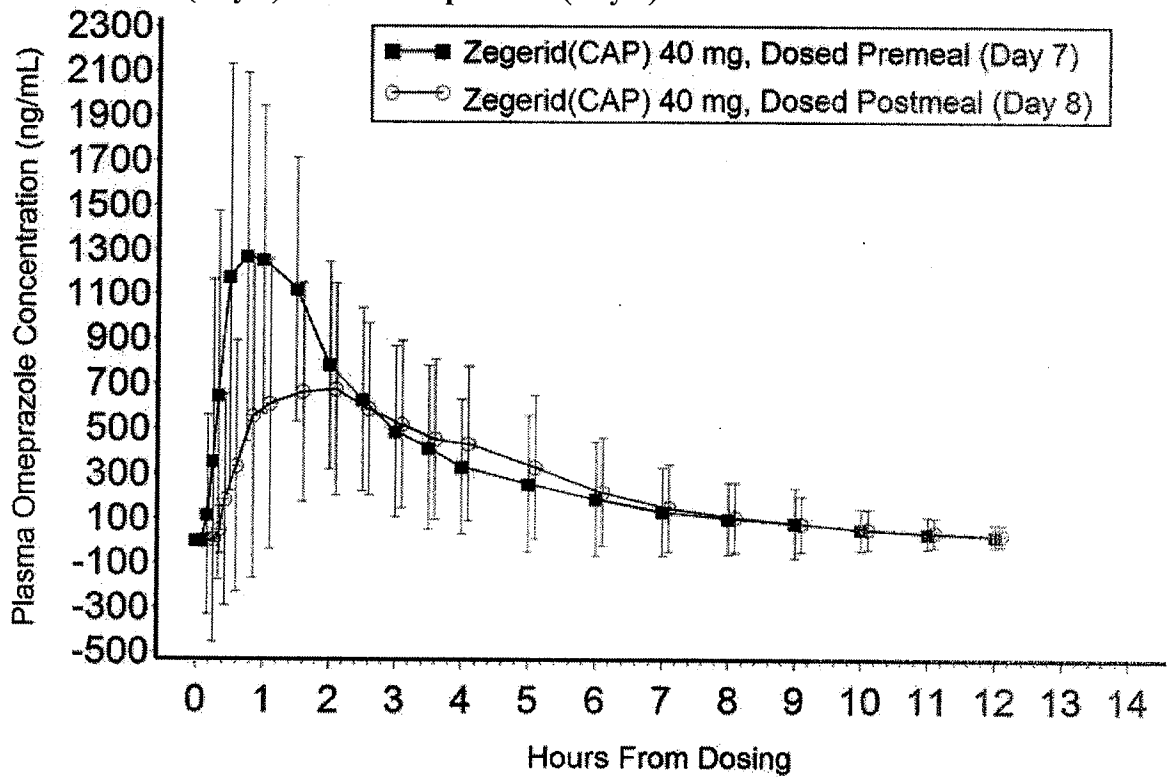


Table 4. Cumulative Integrated Gastric Acidity with Zegerid IR 40 mg Capsule 40 and Prilosec DR 40 mg Capsule

	Integrated Gastric Acidity (mmol*hr/L)		Zegerid(CAP)/Prilosec (%)
Assessment	**Zegerid(CAP) 40 mg**	**Prilosec 40 mg**	**By-Subject Ratios**
Baseline			
Period 1	2493 (1969 - 2607)	2496 (2240 - 3308)	
Period 2	2087 (1517 - 2830)	2036 (1782 - 2290)	
Day 1			
Period 1	1379 (547 - 1882)	1103 (821 - 1593)	
Period 2	1540 (938 - 1628)	1082 (433 - 1584)	
Day 7			
Period 1	685 (359 - 933)	568 (5 - 674)	
Period 2	538 (32 - 891)	557 (218 - 881)	
Percent Decrease from Baseline* to:			
Day 1	45 (5 - 71)	56 (28 - 70)	85 (29 - 105)
Day 7	**77 (58 - 94)**	**79 (69 - 98)**	**97 (83 - 105)**

Figure 4. Cumulative Integrated Gastric Acidity with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

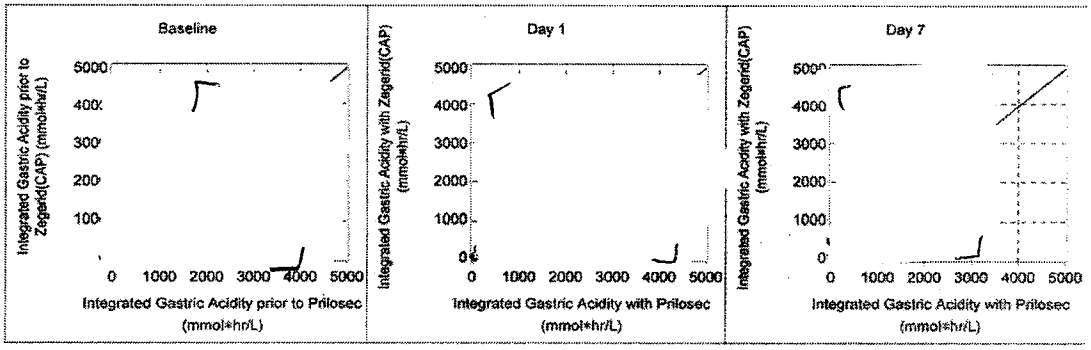


Figure 5. Cumulative Integrated Gastric Acidity with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7

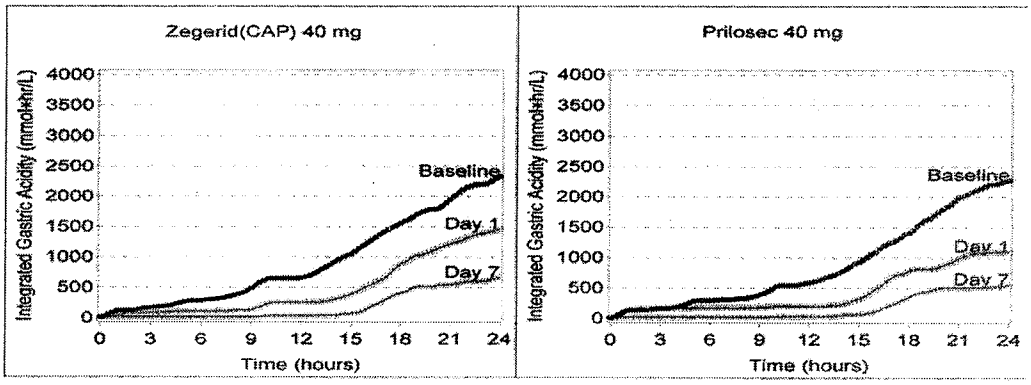


Table 5. Mean Gastric Acid Concentration with Zegerid IR 40 mg Capsule 40 and Prilosec DR 40 mg Capsule

	Mean Gastric Acid Concentration (mM)	
Assessment	**Zegerid(CAP) 40 mg**	**Prilosec 40 mg**
Baseline		
Period 1	104	104
	(82 - 109)	(93 - 138)
Period 2	87	85
	(63 - 118)	(74 - 95)
Day 1		
Period 1	57	46
	(23 - 78)	(34 - 66)
Period 2	64	45
	(39 - 68)	(18 - 66)
Day 7		
Period 1	29	24
	(15 - 39)	(0 - 28)
Period 2	22	23
	(1 - 37)	(9 - 37)

Figure 6. Mean Gastric Acid Concentration with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

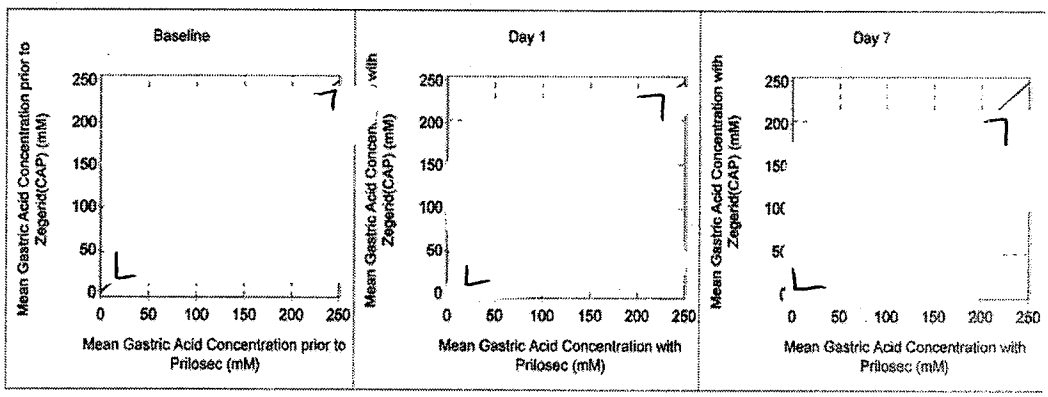


Figure 7. Mean Gastric Acid Concentration with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7

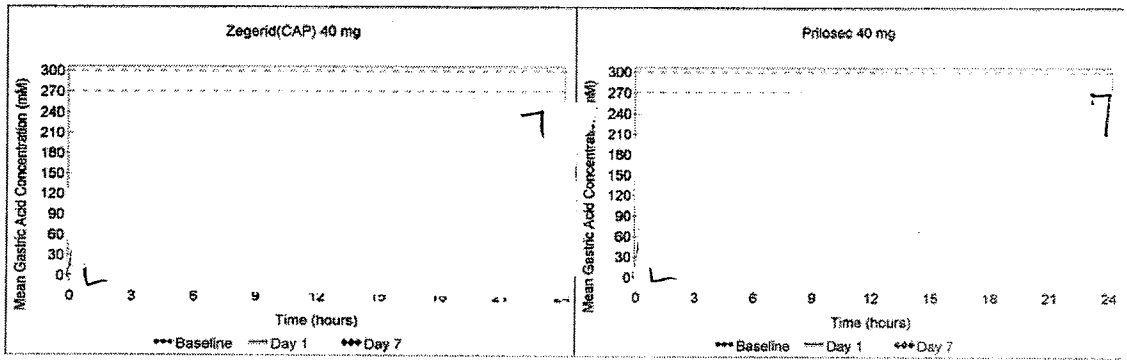


Table 6. Median Gastric pH with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule

	Median Gastric pH	
Assessment	**Zegerid(CAP) 40 mg**	**Prilosec 40 mg**
Baseline		
Period 1	1.06	1.00
	(1.00 - 1.28)	(0.83 - 1.11)
Period 2	1.05	1.15
	(0.86 - 1.50)	(1.06 - 1.21)
Day 1		
Period 1	2.76	4.09
	(1.48 - 4.85)	(1.37 - 4.76)
Period 2	2.42	3.85
	(1.34 - 3.72)	(1.54 - 5.05)
Day 7		
Period 1	4.73	5.43
	(4.16 - 5.36)	(3.92 - 5.89)
Period 2	4.96	5.00
	(4.05 - 5.85)	(4.49 - 5.47)

Figure 8. Mean Gastric Acid Concentration with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

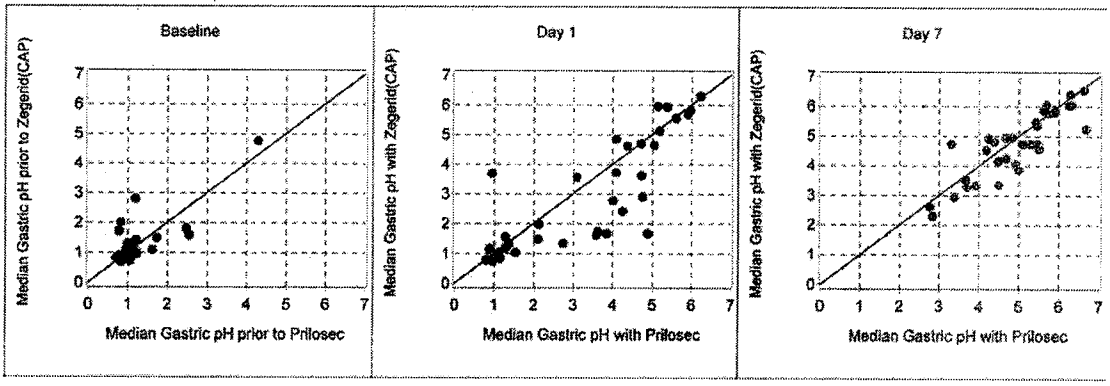


Figure 9. Mean Gastric Acid Concentration with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule on Days 1 and 7

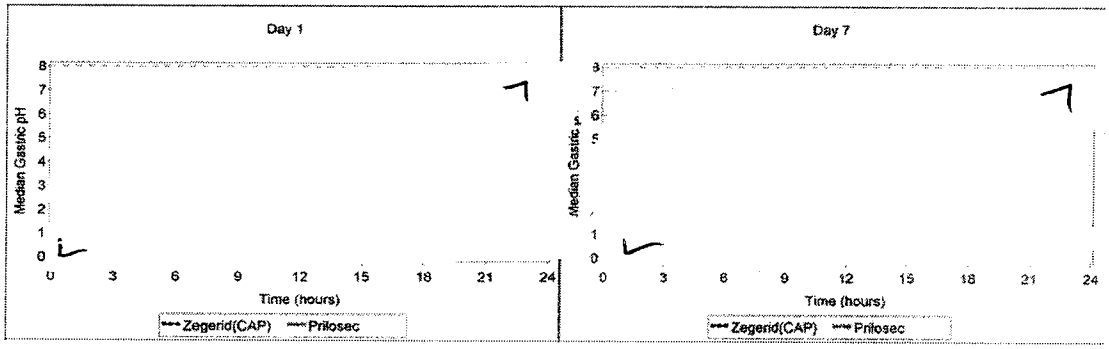


Table 7. Percent Time Gastric pH ≤ 4 with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule

	Percent Time Gastric pH ≤ 4	
Assessment	**Zegerid(CAP) 40 mg**	**Prilosec 40 mg**
Baseline		
Period 1	80	85
	(78 - 94)	(82 - 93)
Period 2	86	86
	(73 - 94)	(70 - 87)
Day 1		
Period 1	55	49
	(35 - 73)	(46 - 76)
Period 2	62	55
	(51 - 76)	(33 - 72)
Day 7		
Period 1	42	32
	(24 - 50)	(4 - 49)
Period 2	39	42
	(16 - 50)	(21 - 46)

Figure 10. Percent Time Gastric pH ≤ 4 with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

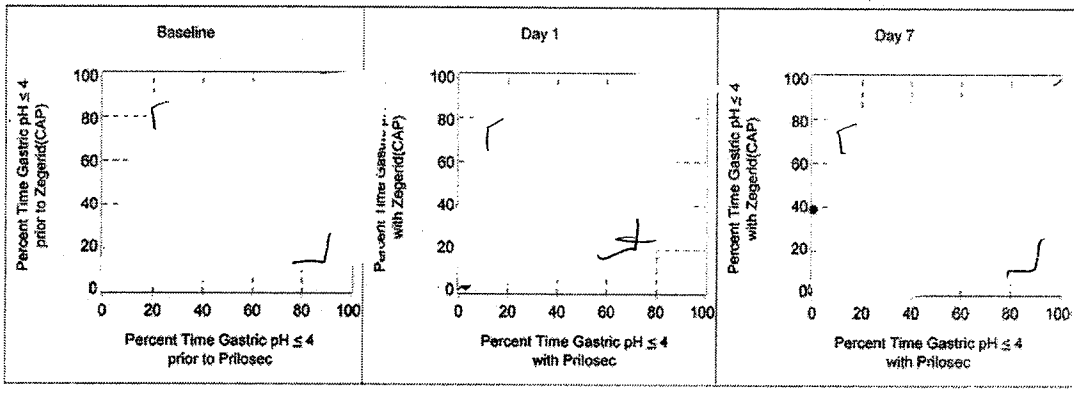
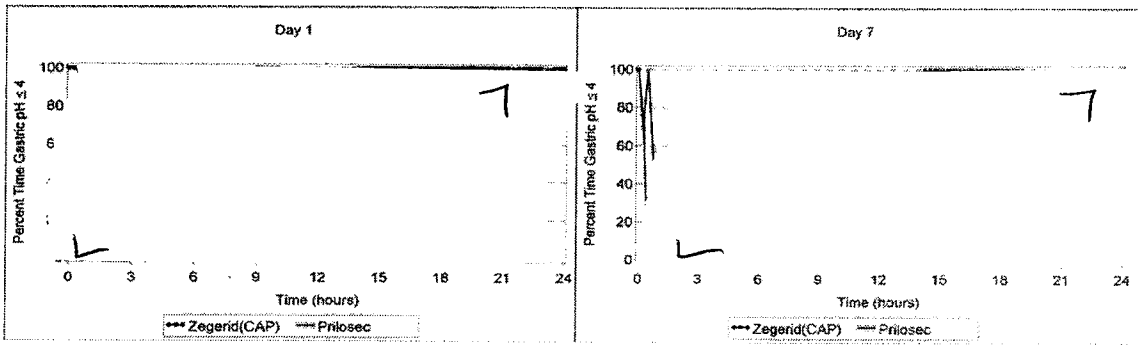


Figure 11. Percent Time Gastric pH ≤ 4 with Zegerid IR 40 mg Capsule and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects



NDA 21-849 for Zegerid IR 20 and 40 mg Capsules

Appendix 3

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-849**	**Brand Name**	**Zegerid**
OCPB Division (I, II, III)	**II**	**Generic Name**	**omeprazole**
Medical Division	**Gastrointestinal and Coagulation**	**Drug Class**	**Gastric Acid Suppressant**
OCPB Reviewer	**Albert Chen**	**Indication(s)**	**Treatment of gastric and Duodenal ulcers/erosive esophagitis/GERD**
OCPB Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Capsules**
		Dosing Regimen	**20 and 40 mg qd**
Date of Submission	**4/27/05**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**12/23/05**	**Sponsor**	**Santarus**
PDUFA Due Date	**2/27/06**	**Priority Classification**	**Standard**
Division Due Date	**12/27/06**		

1.1.1.1.1.1.1.1 Clin. Pharm. and Biopharm. 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			
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) -				
Healthy Volunteers-				
single dose:	x	OME-IR (CAP)-C01 & OME-IR (CAP) C02		OME-IR (CAP) C01 tested SD/MD PK and PD of 20 mg strength relative to Prilosec capsules OME-IR (CAP) C02 tested SD/MD PK and PD of 40 mg strength relative to Prilosec capsules
multiple dose:	x	OME-IR (CAP)-C01 & OME-IR (CAP) C02		
Patients-				
single dose:				
multiple dose:				
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 1	[redacted]	OME-IR (CAP)-C01 & OME-IR (CAP) C02		
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:				
alternate formulation as reference:		OME-IR (CAP)-C01 & OME-IR (CAP) C02		Prilosec capsules is the reference treatment
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	OME-IR (CAP) C02		Effect of food tested on the 40 mg strength
Dissolution:	x			Missing dissolution data on biobatches
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	**2**		

Appears This Way
On Original

Filability and QBR comments				
	"X" if yes	1.1.1.1.1.1.1.1.1 Comments		
Application filable ?	x	This is a 505 b(2) application. Data from two studies (OME-IR (CAP)-C01 & OME-IR (CAP) C02) investigating the PK/PD, bioavailability relative to the listed drug product (Prilosec capsules), and food effect was submitted. Clinical trials were not conducted in support of the application i.e., NDA is Clin. Pharm. & Biopharm. Based. As such, studies C01 and C02 are pivotal and DSI inspection of study C02 (higher strength) is warranted		
Comments sent to firm ?		IR letter will be sent out for the missing dissolution data on biobatches used in the above 2 PK studies that needs to be submitted for review.		
QBR questions (key issues to be considered)		• Are the capsules adequately linked to the Prilosec capsules in terms of the pharmacokinetics and pharmacodynamic data? • Is there a significant effect of food that requires timing of dosage administration? • Is the *in vitro* release method and specification proposed for the product appropriate?		
Other comments or information not included above				
Primary reviewer Signature and Date		Appears This Way On Original		
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/

Tien-Mien Chen
2/1/2006 12:07:19 PM
BIOPHARMACEUTICS

Dennis Bashaw
2/1/2006 12:15:53 PM
BIOPHARMACEUTICS

Appears This Way
On Original

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-849**	**Brand Name**	**Zegerid**
OCPB Division (I, II, III)	**II**	**Generic Name**	**omeprazole**
Medical Division	**Gastrointestinal and Coagulation**	**Drug Class**	**Gastric Acid Suppressant**
OCPB Reviewer	**Albert Chen**	**Indication(s)**	**Treatment of gastric and Duodenal ulcers/erosive esophagitis/GERD**
OCPB Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Capsules**
		Dosing Regimen	**20 and 40 mg qd**
Date of Submission	**4/27/05**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**12/23/05**	**Sponsor**	**Santarus**
PDUFA Due Date	**2/27/06**	**Priority Classification**	**Standard**
Division Due Date	**12/27/06**		

Clin. Pharm. and Biopharm. 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**			
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) -				
Healthy Volunteers-				
single dose:	x	OME-IR (CAP)-C01 & OME-IR (CAP) C02		OME-IR (CAP) C01 tested SD/MD PK and PD of 20 mg strength relative to Prilosec capsules OME-IR (CAP) C02 tested SD/MD PK and PD of 40 mg strength relative to Prilosec capsules
multiple dose:	x	OME-IR (CAP)-C01 & OME-IR (CAP) C02		
Patients-				
single dose:				
multiple dose:				
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 1	[redacted]	OME-IR (CAP)-C01 & OME-IR (CAP) C02		
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:				
alternate formulation as reference:		OME-IR (CAP)-C01 & OME-IR (CAP) C02		Prilosec capsules is the reference treatment
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	OME-IR (CAP) C02		Effect of food tested on the 40 mg strength
Dissolution:	x			Missing dissolution data on biobatches
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	2		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	x	This is a 505 b(2) application. Data from two studies (OME-IR (CAP)-C01 & OME-IR (CAP) C02) investigating the PK/PD, bioavailability relative to the listed drug product (Prilosec capsules), and food effect was submitted. Clinical trials were not conducted in support of the application i.e., NDA is Clin. Pharm. & Biopharm. Based. As such, studies C01 and C02 are pivotal and DSI inspection of study C02 (higher strength) is warranted		
Comments sent to firm ?		IR letter will be sent out for the missing dissolution data on biobatches used in the above 2 PK studies that needs to be submitted for review.		
QBR questions (key issues to be considered)	• Are the capsules adequately linked to the Prilosec capsules in terms of the pharmacokinetics and pharmacodynamic data? • Is there a significant effect of food that requires timing of dosage administration? • Is the *in vitro* release method and specification proposed for the product appropriate?			
Other comments or information not included above	Appears This Way On Original			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Appears This Way
On Original

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

/s/

Tien-Mien Chen
7/18/05 11:06:55 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/18/05 02:45:48 PM
BIOPHARMACEUTICS
DSI inspection request of study CAP-CO2 was signed off in DFS on 6/16/05