Clinical Study Report Synopsis

Drug Substance	Esomeprazole
Study Code	3691 (D961FC00007)
Edition Number	Revised Final Report
Date	17 May 2010

A Phase I, Open-Label, Randomized, Single-Centre, 3-Way Crossover Bioequivalence Study Comparing a Fixed Dose Combination Capsule of Esomeprazole 40 mg and Acetylsalicylic Acid 325 mg with Free Combinations of Esomeprazole Capsule 40 mg and Acetylsalicylic Acid Tablet 325 mg and Esomeprazole Tablet 40 mg and Acetylsalicylic Acid Tablet 325 mg After Single Oral Administration Under Fed Conditions in Healthy Male and Female Subjects

Study dates: First subject enrolled: 14 September 2009
Last subject last visit: 22 October 2009

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Study No. 3691 (D961FC00007) was a single-centre, single-country study conducted at Biovail Contract Research, Toronto ON Canada.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate whether a fixed dose combination of esomeprazole 40 mg/ASA 325 mg capsule (FDC) is bioequivalent to free combinations of an esomeprazole clinical trial capsule (CTC) 40 mg and an ASA tablet 325 mg, and an esomeprazole Multiple Unit Pellet System (MUPS) tablet 40 mg and an acetylsalicylic acid tablet 325 mg, after single oral administration under fed conditions in healthy male and female subjects. Bioequivalence was investigated with regard to esomeprazole component of the three treatments.	AUC_{0-t}, AUC_{0-inf}, and C_{max}	Pharmacokinetic
Secondary	**Secondary**	
To evaluate the pharmacokinetic (PK) properties of esomeprazole after single dose administration of esomeprazole 40 mg/ASA 325 mg combination capsule and free combinations of esomeprazole capsule 40 mg + ASA tablet 325 mg and esomeprazole tablet 40 mg + ASA tablet 325 mg.	AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{½}$	Pharmacokinetic
To evaluate the safety and tolerability of esomeprazole in combination with low dose ASA.	Analysis of adverse events, physical examinations, vital signs and electrocardiogram measurements, and laboratory evaluations	Safety

Study design

The study followed a randomized, 3-way crossover, open-label, single-dose design in 78 normal, healthy, non-smoking male and female subjects (with the objective of having at least 69 subjects complete the study) under fed conditions.

Target subject population and sample size

The study drug (esomeprazole and low-dose ASA in a combination product) is intended for patients receiving low-dose ASA treatment for cardiovascular or cerebrovascular protection

and who are at risk of developing gastrointestinal symptoms and ulcers as a result of this treatment.

This bioequivalence study was conducted in 78 normal, healthy, non-smoking male and female subjects within the age range of 20 to 50 years. Sixty-nine subjects, 68 of whom completed the study, and 1 for whom there were sufficient data to allow for a meaningful analysis were included in the pharmacokinetic and statistical analyses. The sample size of 69 was calculated based on an assumed true ratio of geometric means of 1.05 and on an expected within-subject standard deviation of 0.40 for ln(AUC), derived using data from previous pharmacokinetic studies with Nexium under fed conditions.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Treatment A (test): 1 Esomeprazole 40 mg/ASA 325 mg Fixed Dose Combination (FDC) Capsule, administered orally (Lot # 09-001014AZ, manufactured by AstraZeneca Canada Inc; Treatment Dose = 40 mg of esomeprazole and 325 mg of ASA)

Treatment B (reference): 1 Esomeprazole 40 mg Clinical Trial Capsule (CTC), administered orally with 1 ASA Tablet 325 mg (Esomeprazole: Lot # 09-000607AZ, manufactured by AstraZeneca Canada Inc; ASA: Lot #291339F, manufactured by Bayer Inc, Toronto Canada; Treatment Dose = 40 mg of esomeprazole and 325 mg of ASA)

Treatment C (reference): 1 Esomeprazole 40 mg Multiple Unit Pellet System (MUPS) Tablet, administered orally with 1 ASA Tablet 325 mg (Esomeprazole: Lot # LF11815, manufactured by AstraZeneca Canada Inc; ASA: Lot #291339F, manufactured by Bayer Inc, Toronto Canada; Treatment Dose = 40 mg of esomeprazole and 325 mg of ASA)

Duration of treatment

The single-dose study consisted of a screening visit (no more than 30 days before the first drug administration) and three 3-day study periods. Subjects were admitted to the Comstock clinic the day before dosing, and remained until the 24.00-hour post-dose blood draw of each period, at which time they were allowed to leave the clinic. There was a 1-week washout period between study treatments. An End-of-Study evaluation was conducted during the same visit as the last pharmacokinetic (PK) blood-draw of Period III, after completion of all clinical study activities.

Statistical methods

Using General Linear Model (GLM) procedures in Statistical Analysis System (SAS), analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and on untransformed T_{max} and $t_{½}$ at the significance level of 0.05. The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval (90% CI) were calculated based on the difference in the Least Squares Means of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} between the test and reference formulations. The

potency corrected 90% CI were presented for AUC_{0-t}, AUC_{0-inf}, and C_{max}. T_{max} was analyzed using nonparametric methods.

Subject population

One hundred thirty eight (138) normal, healthy, non-smoking male and female volunteers were screened for the study, 78 of whom were randomized in Period I. Five (5) subjects withdrew from the study because of adverse events (AEs), and 5 subjects withdrew from the study for personal reasons. Demographic data for all subjects who participated in the study, as well as the data for subjects included in each treatment group were similar.

Summary of pharmacokinetic results

Table S2 Comparison of pharmacokinetic parameters of esomeprazole in healthy male and female subjects for Treatments A and B

Parameter	Number of subjects in comparison	Geometric least square mean (95% CI)		Ratio (FDC/CTC)	90% CI of the ratio	Intra-subject CV (%)
		FDC (A)	CTC (B)			
Potency uncorrected data						
AUC_{0-t}	68	4.21 (3.86, 4.58)	3.30 (3.02, 3.60)	127.62%	115.19% to 141.39%	37.34%
AUC_{0-inf}	63	4.44 (4.09, 4.82)	3.62 (3.33, 3.93)	122.59%	111.19% to 135.15%	33.10%
C_{max}	68	1.25 (1.11, 1.40)	0.93 (0.83, 1.05)	133.70%	116.25% to 153.78%	52.47%
Potency corrected data						
AUC_{0-t}	68	N/AP	N/AP	126.33%	114.02% to 139.96%	N/AP
AUC_{0-inf}	63	N/AP	N/AP	121.35%	110.07% to 133.78%	N/AP
C_{max}	68	N/AP	N/AP	132.35%	115.07% to 152.23%	N/AP

Treatment A: 1 Esomeprazole 40 mg/ASA 325 mg FDC

Treatment B: 1 Esomeprazole Clinical Trial Capsule 40 mg and 1 ASA Tablet 325 mg

Table S3 Comparison of pharmacokinetic parameters of esomeprazole in healthy male and female subjects for Treatments A and C

Parameter	Number of subjects in comparison	Geometric least square mean (95% CI)		Ratio (FDC/MUPS)	90% CI of the ratio	Intra-subject CV (%)
		FDC (A)	MUPS (C)			
Potency uncorrected data						
AUC_{0-t}	69	4.21 (3.86, 4.58)	4.55 (4.17, 4.96)	92.46%	83.50% to 102.39%	37.34%
AUC_{0-inf}	63	4.44 (4.09, 4.82)	4.73 (4.36, 5.12)	93.91%	85.23% to 103.47%	33.10%
C_{max}	69	1.25 (1.11, 1.40)	1.44 (1.28, 1.62)	86.62%	75.36% to 99.56%	52.47%
Potency corrected data						
AUC_{0-t}	69	N/AP	N/AP	93.40%	84.34% to 103.43%	N/AP
AUC_{0-inf}	63	N/AP	N/AP	94.86%	86.09% to 104.52%	N/AP
C_{max}	69	N/AP	N/AP	87.49%	76.12% to 100.57%	N/AP

Treatment A: 1 Esomeprazole 40 mg/ASA 325 mg FDC

Treatment C: 1 Esomeprazole MUPS Tablet 40 mg and 1 ASA Tablet 325 mg

Table S4 Summary statistics of pharmacokinetic parameters of Esomeprazole in healthy male and female subjects for Treatments A, B, and C

Pharmacokinetic Parameter	Geometric mean (%CV) Arithmetic mean ± SD		
	Treatment A (n=69)	Treatment B (n=68)	Treatment C (n=69)
AUC_{0-t} (µmol•hr/L)	4.18 (87.61) 6.13±5.37	3.24 (99.54) 4.93±4.91	4.53 (83.58) 6.51±5.44
AUC_{0-inf} (µmol•hr/L)	4.61 (84.56) 6.60±5.58 [b]	3.71 (94.43) 5.34±5.04 [b]	5.00 (79.66) 6.92±5.51 [c]
C_{max} (µmol/L)	1.24 (72.08) 1.68±1.21	0.92 (73.11) 1.29±0.94	1.44 (70.43) 1.88 ± 1.32
T_{max} (hr) [a]	6.00 (3.00-11.08)	6.05 (3.00-11.00)	4.50 (2.00-9.00)
$t_{½}$ (hr)	1.41±0.62 [b]	1.40±0.70 [b]	1.40±0.62 [c]

Treatment A: 1 Esomeprazole 40 mg/ASA 325 mg FDC Capsule

Treatment B: 1 Esomeprazole CTC 40 mg and 1 ASA Tablet 325 mg

Treatment C: 1 Esomeprazole MUPS Tablet 40 mg and 1 ASA Tablet 325 mg

[a] median (min-max)

[b] n=63

[c] n=65

Summary of safety results

Nineteen (19) subjects experienced a total of 28 AEs during the study. The most frequent AEs are expressed as fractions, relative to the total number of AEs experienced after each treatment. After treatment with 1 Esomeprazole 40 mg/ASA 325 mg FDC Capsule, the most frequent AE was somnolence (4/9). After treatment with 1 Esomeprazole CTC 40 mg and 1 ASA Tablet 325 mg, the most frequent AE was somnolence (3/11). After treatment with 1 Esomeprazole MUPS Tablet 40 mg and 1 ASA Tablet 325 mg, the most frequent AEs were the following: stomach discomfort (2/8), influenza like illness (2/8), and somnolence (2/8). All adverse events were mild in intensity, and resolved with no action taken. No AEs were reported after the end-of-study exam. The number and type of adverse events collected in this study were consistent with expectations for a normal, healthy subject population, and there were no significant differences in the number of AEs reported between groups. The Principal Investigator or Sub-investigator assessed that there was a reasonable possibility that 17 AEs were caused by the investigational product. All subjects who experienced AEs during this study recovered completely. All of the subjects who experienced AEs during this study were able to complete the study, with the exception of 5 subjects who withdrew from the study because of AEs. No serious adverse events (SAEs) were reported.