A Phase I, Open-label, Randomized, Single-center, 2-way Crossover Food interaction Study to Assess the Effect of Food on the Pharmacokinetics of the Fixed Dose Combination Capsule of Esomeprazole 20 mg/Acetylsalicylic Acid 81 mg

Study dates:

First subject enrolled: 27 July 2010
Last subject last visit: 30 August 2010

Phase of development:

Clinical pharmacology (I)

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

Study center

The study was conducted at a single center; Quintiles Phase I Unit, Overland Park, Kansas, United States.

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 the effects of food, in comparison to fasting conditions, on the extent and rate of absorption of acetylsalicylic acid and esomeprazole after a single-dose administration of esomeprazole 20 mg/ acetylsalicylic acid 81 mg fixed-dose combination in healthy volunteers	AUC, $AUC_{(0-t)}$, and C_{max}	Pharmacokinetic
Secondary	**Secondary**	
To investigate pharmacokinetics of acetylsalicylic acid and esomeprazole	t_{max} and $t_{1/2\lambda z}$ under fed and fasted conditions	Pharmacokinetic
To investigate pharmacokinetics of acetylsalicylic acid metabolite salicylic acid	AUC, $AUC_{(0-t)}$, C_{max}, t_{max} and $t_{1/2\lambda z}$ under fed and fasted conditions	Pharmacokinetic
To assess the safety and tolerability of esomeprazole 20mg/acetylsalicylic acid 81 mg fixed-dose combination	adverse events, physical examination, pulse, blood pressure, weight, and laboratory variables	safety

Study design

This study was performed as an open-label, randomized, 2-way crossover trial. In each study period a single dose of esomeprazole 20 mg/acetylsalicylic acid 81 mg fixed-dose combination was given after food or during fasting conditions. Under Treatment A, volunteers received esomeprazole 20 mg/acetylsalicylic acid 81 mg fixed-dose combination after a 10-hour fast; under Treatment B volunteers received esomeprazole 20 mg/acetylsalicylic acid 81 mg fixed-dose combination, 30 minutes after start of a high-fat, high-calorie breakfast. Based on a randomization schedule, volunteers were assigned to 1 of 2 sequences of dosing treatments (Sequence AB or Sequence BA).

Target subject population and sample size

Healthy male and female volunteers from 18 to 50 years of age inclusive.

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

Esomeprazole 20 mg/acetylsalicylic acid 81 mg fixed-dose combination (batch number 10-002683AZ) was administered orally as a capsule once in the morning after food or under fasting conditions.

Duration of treatment

The duration of volunteer participation was approximately 36 days. This included a 21-day pre-entry visit for confirmation of eligibility and signing of informed consent form, randomization to a 1-day Treatment Period 1, at least a 6-day washout period, a 1-day Treatment Period 2, and a 5 to 7 day follow-up visit.

Statistical methods

The plasma concentrations of esomeprazole, acetylsalicylic acid, and salicylic acid and the derived pharmacokinetic parameters were summarized by treatment using descriptive statistics.

The sample size calculation was based on expected within-volunteer standard deviations of $\ln(AUC)$ and $\ln(C_{max})$ of 0.25 and 0.35, respectively. Under these assumptions, with 20 evaluable volunteers, the 90% confidence interval for the ratio of the true means of AUC (AUC after food/AUC fasting) should range from 86% to 117% of the estimated ratio of the means. The coverage probability for this calculation was 80%. The corresponding confidence interval for the ratio for C_{max} should range from 81% to 124% of the estimated mean.

To assess the effect of food, the geometric means of the primary pharmacokinetic parameters of acetylsalicylic acid, salicylic acid, and esomeprazole in the fed treatment arm were compared to that of the fasted treatment arm. The primary pharmacokinetic parameters AUC, $AUC_{(0-t)}$, and C_{max} were analyzed on log scale using a linear mixed-effect analysis-of-variance model with fixed effects for sequence, period, and treatment, and random effect for volunteer nested within sequence. Transformed back from the logarithmic scale, geometric means together with 2-sided 95% confidence intervals for AUC, $AUC_{(0-t)}$, and C_{max} were estimated. Ratios of geometric means together with 2-sided 90% confidence intervals for Treatment B/Treatment A (fed/fasted treatment) were estimated.

The parameter t_{max} was analyzed nonparametrically using the Wilcoxon signed-rank test which does not account for period effects. The median differences and 90% confidence intervals for the difference of t_{max} between fed and fasted treatments were calculated. Confidence intervals were estimated using the method of Hahn and Meeker.

The safety data were summarized by treatment using descriptive statistics or frequency counts in tables and listings.

Subject population

There were a total of 23 volunteers, all of them randomly assigned to 1 of 2 dosing sequences (either esomeprazole 20 mg/acetylsalicylic acid 81 mg fixed-dose combination after a 10-hour fast [Treatment A] or esomeprazole 20 mg/acetylsalicylic acid 81 mg fixed-dose combination 30 minutes after the start of a high-fat, high-calorie breakfast [Treatment B]). Twenty-two volunteers completed the study per protocol, and 1 volunteer (E0001052) discontinued due to lost-to-follow-up after only receiving study medication under fasted condition. There were 10 women (43.5%) and 13 men (56.5%); 14 volunteers were white (60.9%), 8 volunteers were black (34.8%), and 1 volunteer (4.3%) was American Indian or Alaska native. The mean age at screening was 27.6 ±6.35 years (range from 20 to 46 years). Medical history was unremarkable and the use of concomitant medications during the study was minimal.

Summary of efficacy results - not applicable

Summary of pharmacokinetic results

The results of the statistical comparisons between treatments showed that administration with food reduced overall acetylsalicylic acid exposure approximately 9% to 12% and maximum acetylsalicylic acid plasma concentration approximately 38%. The 90% confidence intervals for AUC, $AUC_{(0-t)}$ and C_{max} least-squares mean ratios were not contained within the limits of 80% to 125%. In addition, median t_{max} was delayed 1.25 hours when administered with food.

Statistical comparison of key acetylsalicylic acid pharmacokinetic parameters

Parameter			Geometric		Ratio	
(units)	Treatment	N	LS Mean	Pair	(%)	90% CI
AUC	Fasted	16	4.806			
(μmol·h/L)	Fed	6	4.394	Fed/Fasted	91.44	(74.11, 112.84)
$AUC_{(0-t)}$	Fasted	23	4.137			
(μmol·h/L)	Fed	22	3.66	Fed/Fasted	88.46	(77.24, 101.31)
C_{max}	Fasted	23	3.428			
(μmol/L)	Fed	22	2.124	Fed/Fasted	61.98	(52.80, 72.75)
			Median	Pair	Difference	90% CI
t_{max}	Fasted	23	0.5			
(h)	Fed	22	1.75	Fed-Fasted	1.25	(0.73, 2.22)

CI confidence interval; LS least-squares; N number of volunteers/observations.

The results of the statistical comparisons between treatments showed that administration with food reduced overall esomeprazole exposure approximately 23 to 32% and maximum esomeprazole plasma concentration approximately 36%. The 90% confidence intervals for AUC, $AUC_{(0-t)}$ and C_{max} least-squares mean ratios were not contained within the limits of 80% to 125%. In addition, median t_{max} was delayed 2.75 hours when administered with food.

Statistical comparison of key esomeprazole pharmacokinetic parameters

Parameter (units)	Treatment	N	Geometric LS Mean	Pair	Ratio (%)	90% CI
AUC (μmol·h/L)	Fasted	21	1.685			
	Fed	16	1.306	Fed/Fasted	77.49	(65.68, 91.42)
$AUC_{(0-t)}$ (μmol·h/L)	Fasted	23	1.417			
	Fed	22	0.9615	Fed/Fasted	67.86	(58.09, 79.27)
C_{max} (μmol/L)	Fasted	23	0.7013			
	Fed	22	0.4513	Fed/Fasted	64.35	(50.77, 81.57)
			Median	**Pair**	**Difference**	**90% CI**
t_{max} (h)	Fasted	23	2.00			
	Fed	22	5.00	Fed-Fasted	2.75	(2.15, 3.50)

CI confidence interval; LS least-squares; N number of volunteers/observations.

The results of the statistical comparisons between treatments showed that administration with food reduced overall salicylic acid exposure approximately 9% to 13% and maximum salicylic acid plasma concentration approximately 12%. The 90% confidence intervals for the AUC and $AUC_{(0-t)}$ least-squared mean ratios were contained within the limits of 80 to 125%. The 90% confidence interval for the C_{max} least-squared mean ratio was not contained within the limits of 80% to 125%. In addition, median t_{max} was delayed just over 1 hour when administered with food.

Statistical comparison of key salicylic acid pharmacokinetic parameters

Parameter (units)	Treatment	N	Geometric LS Mean	Pair	Ratio (%)	90% CI
AUC (μmol·h/L)	Fasted	21	124.7			
	Fed	17	113.5	Fed/Fasted	90.98	(88.23, 93.81)
$AUC_{(0-t)}$ (μmol·h/L)	Fasted	23	106.4			
	Fed	22	92.82	Fed/Fasted	87.25	(83.61, 91.04)
C_{max} (μmol/L)	Fasted	23	23.83			
	Fed	22	20.92	Fed/Fasted	87.78	(78.40, 98.29)
			Median	**Pair**	**Difference**	**90% CI**
t_{max} (h)	Fasted	23	2.00			
	Fed	22	3.00	Fed-Fasted	1.13	(0.50, 1.50)

CI confidence interval; LS least-squares; N number of volunteers/observations.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

There were no deaths or serious adverse events reported during study conduct and no volunteers discontinued from the study due to an adverse event. There were no other significant adverse events of interest. Ecchymosis was the most frequently reported treatment-emergent adverse event (2 volunteers). All other treatment-emergent adverse events were reported by only 1 volunteer. All treatment-emergent adverse events were considered by the Investigator to be mild in intensity and not related to study drug.

There were no clinically important changes in clinical laboratory findings, vital signs, or physical examination findings during the study.