AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Esomeprazole
Study Code	D9617L00001
Edition Number	2.0
Date	21 Jul 2009

A multicenter, randomized, double-blind, double-dummy, parallel-group, 8 week comparative efficacy and safety study of esomeprazole 20 mg qd versus ranitidine 150 mg bid in patients with a NSAID-associated gastric ulcer when daily NSAID is continued

Study dates: First patient enrolled: 31 Mar 2006
Last patient completed: 17 Nov 2008

Phase of development: Therapeutic confirmatory (III)

Sponsor's Responsible Medical Officer:

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

Study centre(s)

The study was conducted at 24 investigational sites in China. The first patient was enrolled on 31 Mar 2006, the last patient was completed on 17 Nov 2008.

Publications

None at the time of writing this report.

Objectives

Primary objective

- To assess the efficacy of esomeprazole 20 mg qd and ranitidine 150 mg bid through 4 weeks of treatment for the healing of gastric ulcers in patients receiving daily NSAID therapy. Healing was defined as the absence of gastric ulcers (Ulcers were at least on S stage or absence).

Secondary objectives

- To assess the efficacy of esomeprazole 20 mg qd and ranitidine 150 mg bid through 8 weeks of treatment for the healing of gastric ulcers in patients receiving daily NSAID therapy. Healing was defined as the absence of gastric ulcers (Ulcers were at least on S stage or absence).
- To evaluate the patient symptoms, defined as control of NSAID-associated GI symptoms for up to 8 weeks of treatment with esomeprazole esomeprazole 20 mg qd versus ranitidine 150 mg bid in patients receiving daily NSAID therapy.
- To evaluate Safety and tolerability of esomeprazole 20 mg qd versus ranitidine 150 mg bid when administered for up to 8 weeks to patients receiving daily NSAID therapy.

Study design

The study was carried out as a multicenter, randomized, double-blind, double-dummy, parallel-group, 8 week comparative efficacy and safety study. Patients who had been receiving a stable daily dose of 1 or more NSAIDs for at least 2 weeks and who had an NSAID-associated gastric ulcer (GU) verified by Esophagogastroduodenoscopy (EGD) at baseline were randomized in 18 centers in China. The patients were given esomeprazole 20 mg qd or ranitidine 150 mg bid for up to 8 weeks and were evaluated by EGD at Weeks 4 and 8 of treatment. Patients whose GU(s) are healed at week 4 will leave the study, such patients should finish the week 8 visit contents when they leave the study at week 4 and be considered as healed at week 8.

Target patient population and sample size

The study population was to include approximately 320 patients (approximately 160 subjects per treatment group) who were receiving daily NSAID therapy and had a gastric ulcer≥5 mm in diameter, but < 25 mm at its greatest diameter, at the baseline EGD. However, due to the difficulties encountered during the study implementation, total 217 patients who had been receiving a stable daily dose of 1 or more NSAIDs for at least 2 weeks and who had an NSAID-associated GU verified by EGD at baseline were randomized in 18 centers in China.

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

Esomeprazole tablet 20 mg qd oral administration for 8 weeks.

Ranitidine 150 mg bid oral administration for 8 weeks.

Duration of treatment

Eligible subjects were treated for up to 8 weeks.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

– Primary outcome variable:

The proportion of subjects whose gastric ulcer(s) was (were) healed at Week 4 after treatment with esomeprazole 20 mg qd and ranitidine 150 mg bid in patients receiving daily NSAID therapy

– Secondary outcome variables:

The proportion of subjects whose gastric ulcer(s) was (were) healed at Week 8 after treatment with esomeprazole 20 mg qd and ranitidine 150 mg bid in patients receiving daily NSAID therapy

The resolution rate of symptoms at week 4 and week 8 after treatment with esomeprazole 20 mg qd and ranitidine 150 mg bid in patients receiving daily NSAID therapy

The proportion of patients whose DU(s) was (were) healed at Week 4 and Week 8 after treatment with esomeprazole 20 mg qd and ranitidine 150 mg bid in patients receiving daily NSAID therapy

The relief rate of symptoms at week 4 and week 8 after treatment with esomeprazole 20 mg qd and ranitidine 150 mg bid in patients receiving daily NSAID therapy

Ad hoc analysis: The proportion of patients whose GU(s) and DU(s) in combination were healed at Week 4 and Week 8 after treatment with esomeprazole 20 mg qd and ranitidine 150 mg bid in patients receiving daily NSAID therapy

Criteria for evaluation - safety (main variables)

Safety and tolerability to the study drug including vital signs (blood pressure and pulse rate), physical examination, electrocardiogram (ECG), adverse events (AEs), and clinical laboratory evaluations

Statistical methods

Analysis on efficacy endpoints were performed for intention to treat (ITT) population defined as all randomized subjects who had taken at least one dose of the treatment and who had at least one gastric ulcer at the baseline endoscopy. Efficacy analysis were also repeated in per protocol (PP) population defined as all ITT subjects without significant protocol violations and major deviations. Analysis on safety endpoints were performed for subjects who take at least one dose of the trial treatment and have post-dose data. Efficacy endpoints were analyzed by randomized treatment and safety endpoints were analyzed by treatment actually received.

In general, the descriptive statistics (number, mean, median, standard deviation, minimum and maximum) were performed for continuous variables. The frequency tables (number and percentage of subjects) were performed for categorical variables.

For the efficacy endpoint, the proportion of subjects who exhibit complete healing of gastric ulcer(s) after 4 weeks and 8 weeks' treatment were summarized and analyzed for both ITT and PP population. Patients with missing healing status were considered as not healed in the analysis. Differences between treatment groups in the GU healing rates at week 4 and week 8 were analyzed using CMH test stratified by baseline ulcer size. All statistical tests were two-sided with the 5% level of significance. Results will be presented in terms of P-value, Mantel-Haenszel RR and corresponding 95% confidence interval. P-value less than 0.05 is considered as statistically significant. To estimate the absolute difference between treatment groups, the results will also be presented in terms of the difference (esomeprazole minus ranitidine) and its associated 95% confidence interval.

The percentage of patients who exhibited resolution of symptoms at Week 4 and Week 8 was analyzed using a CMH test stratified by the baseline severity of each symptom.

Safety endpoints were summarized by treatment received in the safety population. No inferential statistical analysis was done for the safety variables. Descriptive statistics for all Vital signs, ECG, AEs, physical examination, and laboratory measurements were performed.

A sample size of 320 patients (160 randomized patients per group) was needed to provide 80% power to detect a 15% difference in the primary endpoint at a significance level of 0.05 – the healing rate of GU at week 4 (based on the data from global SH-NEN-0005 and SH-NEN-0006 study, the healing rates were 76% for the esomeprazole group (20mg qd) and 61% for the ranitidine group) at week 4.

Subject population

The disposition and demographic and baseline characteristics of the study population are shown in Table S1. The primary reason for exclusion from the PP population was violation of inclusion or exclusion criteria.

Table S1 Subject disposition (completion or discontinuation)

Disposition	**Esomeprazole n (%)**	**Ranitidine n (%)**	**Total n (%)**
Number of patients enrolled			**397**
Number of patients not randomized			178
Number of patients randomized	107(100.0%)	112(100.0%)	219(100.0%)
Number of patients received treatment	107(100.0%)	111(99.1%)	218(99.5%)
Number of patients completed study	97(90.7%)	94(83.9%)	191(87.2%)
Number of patients discontinued	10(9.3%)	18(16.1%)	28(12.8%)
Demographic characteristics (ITT)	Esomeprazole (N=106)	Ranitidine (N=111)	Total (N=217)
Age (years)			
Mean (SD)	49.7 (11.01)	50.9 (10.20)	50.3 (10.60)
Min-Max	19-69	17-69	17-69
Sex			
Male (n (%))	55(51.9%)	58(52.3%)	113(52.1%)
Female (n (%))	51(48.1%)	53(47.7%)	104(47.9%)
Race			
Caucasian (n (%))	0(0.0%)	0(0.0%)	0(0.0%)
Black (n (%))	0(0.0%)	0(0.0%)	0(0.0%)
Oriental (n (%))	106(100.0%)	111(100.0%)	217(100.0%)
Other (n (%))	0(0.0%)	0(0.0%)	0(0.0%)
Baseline characteristics (ITT)	Esomeprazole (N=106) n (%)	Ranitidine (N=111) n (%)	Total (N=217) n (%)
Hp status (by histology)			
Negative	40(38.8%)	45(41.7%)	85(40.3%)
Positive	63(61.2%)	63(58.3%)	126(59.7%)
GU			
Inactive [a]	0	0	0

Disposition	Esomeprazole n (%)	Ranitidine n (%)	Total n (%)
Number of patients enrolled			**397**
Active [b]	106(100%)	111(100%)	217(100%)
GU			
Benign	102(99.0%)	109(99.1%)	211(99.1%)
Malignant	1(1.0%)	1(0.9%)	2(0.9%)
Chronic condition			
Rheumatoid arthritis	53 (50.0%)	52 (46.8%)	105 (48.4%)
Osteoarthritis	19 (17.9%)	15 (13.5%)	34 (15.7%)
Ankylosing spondylitis	10 (9.4%)	9 (8.1%)	19 (8.8%)
Baseline NSAID Type			
COX-2 selective NSAID (n (%))	23(21.7%)	21(18.9%)	44(20.3%)
Nonselective NSAID (n (%))	76(71.7%)	78(70.3%)	154(71.0%)
Multiple NSAIDs (n (%))	7(6.6%)	12(10.8%)	19(8.8%)

[a] Inactive: Scarring stage (See Section 5.5.3.2 (a))
[b] Active: Active and/or Healing stage (See Section 5.5.3.2 (a)) and/or pathology diagnosis for biopsy was active
Missing data were not included in the calculation.

Summary of efficacy results

The efficacy evaluation in ITT population demonstrated that the GU healing rate was similar between the Esomeprazole group and Ranitidine group following 4 weeks of treatment in patients who continued to use daily NSAIDs. Esomeprazole group was numerically higher than Ranitidine group in healing rate of GU following 8 weeks of treatment in patients who continued to use daily NSAIDs. Moreover, patients in the Esomeprazole group had higher resolution rates in all GI symptoms compared to Ranitidine group based on investigator symptom assessment at both week 4 and 8. The relief rates in all GI symptoms were similar between two treatment groups at week 4 and 8.

The healing rates of duodenal ulcer was numerically higher in the Esomeprazole group than in the Ranitidine group through both 4 and 8 weeks treatment in the patients with continues to daily NSAIDs administration.

At an ad hoc analysis evaluating GU and DU in combination, esomeprazole was slightly more effective than Ranitidine at Week 8.

Table S2 Summary of Observed Healing Rates

Week	Variable	Esomeprazole n (%)	Ranitidine n (%)
Observed healing rates of GU			
Week 4 (ITT)	Healed	63/106(59.4%)	66/111(59.5%)
	CMH P-value	0.9022	
Week 4 (PP)	Healed	61/100(61.0%)	61/99(61.6%)
	CMH P-value	0.9404	
Week 8 (ITT)	Healed	86(81.1%)	82(73.9%)
	CMH P-value	0.1764	
Observed healing rates of GU (with no imputation of missing values at Week 4)			
Week 4 (ITT)	Healed	63(64.3%)	66(68.8%)
	CMH P-value	0.6501	
Week 8 (ITT)	Healed	86(85.1%)	82(85.4%)
	CMH P-value	0.9760	
Observed healing rates of duodenal ulcer			
Week 4 (ITT)	Healed	14/15 (93.3%)	18/22 (81.8%)
Week 8 (ITT)	Healed	14/15 (93.3%)	16/22 (72.7%)
Observed Healing Rates of GU and Duodenal Ulcer in combination (ad hoc analysis)			
Week 4 (ITT)	Healed	62/106 (58.5%)	64/111 (57.7%)
	CMH P-value	0.8054	
Week 8 (ITT)	Healed	85/106 (80.2%)	77/111 (69.4%)
	CMH P-value	0.0596	

Summary of safety results

Totally 43 patients reported a total of 60 AEs in the study. The percentage of patients who experienced AEs was lower in the Esomeprazole group (16.8%) than in the Ranitidine group (22.7%). The frequency of AEs judged to be related to study drug (attributable AEs) was also lower in the Esomeprazole group (2) than in the Ranitidine group (6). Discontinuation of study treatment due to AEs occurred less frequently in the Esomeprazole group (1.9%) than in the Ranitidine group (4.5%), primarily because of higher discontinuation rates due to GI-related AEs in the Ranitidine group.

There were no deaths reported in the study. A total of 4 SAEs were reported in 4 patients: 2 in the Esomeprazole group, and the other 2 in the Ranitidine group. There were similar

percentages of SAEs between the Esomeprazole (1.9%) and Ranitidine (1.8%) treatment groups, and overall, there were few SAEs in the study and no SAEs were determined as drug related.

The general changes from baseline in lab examination were comparable between both treatment groups and not clinically significant.

Table S3 Overview of Adverse Events (Safety Population)

Category of AEs	**n(%) of patients who had an AE in each category**		
	Esomeprazole (N=107)	**Ranitidine (N=110)**	**Total (N=217)**
Any AE	18 (16.8%)	25 (22.7%)	43 (19.8%)
Study drug related AEs	1 (0.9%)	4 (3.6%)	5 (2.3%)
AEs leading to discontinuation of investigational drug	2 (1.9%)	5 (4.5%)	7 (3.2%)
SAEs	2 (1.9%)	2 (1.8%)	4 (1.8%)
Death	0	0	0
SAEs other than death	2 (1.9%)	2 (1.8%)	4 (1.8%)
Other significant adverse events	0	0	0
	Total number of AEs		
Any AE	21	39	60
Study drug-related AEs	2	6	8
AEs leading to discontinuation of investigational drug	2	8	10
SAEs	2	2	4
Death	0	0	0
SAEs other than death	2	2	4
Other significant adverse events	0	0	0

Table S4 Summary of Number (%) (Cut-off of 1.0%) of Subjects with Adverse Events by Preferred Term (Safety Population)

Preferred Term	Esomeprazole (N=107) n(%)	Ranitidine (N=110) n(%)
Total number of patients with at least one adverse event	18 (16.8%)	25 (22.7%)
Dizziness	0	5 (4.5%)
Gastritis erosive	3 (2.8%)	4 (3.6%)
Alanine aminotransferase increased	2 (1.9%)	0
Aspartate aminotransferase increased	2 (1.9%)	0
Gastric cancer	2 (1.9%)	0
Gastric ulcer	2 (1.9%)	1 (0.9%)
Abdominal pain upper	1 (0.9%)	2 (1.8%)
Upper respiratory tract infection	1 (0.9%)	2 (1.8%)
Duodenal ulcer	0	2 (1.8%)

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