Clinical Study Report Synopsis

Drug Substance	Esomeprazole Magnesium
Study Code	D961RC00002
Edition Number	1
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A Phase III Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial of 14-Day Treatment with Esomeprazole 20 mg Once Daily in Subjects with Frequent Heartburn

Study dates: First subject enrolled: 11 August 2011
Last subject last visit: 24 October 2011

Phase of development: Therapeutic confirmatory (III)

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

Study centers

Subjects were recruited from 10 centers in the United States of America (USA).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To determine the efficacy of esomeprazole 20 mg qd over a 14-day regimen for the treatment of frequent heartburn in subjects who are likely to self-treat with non-prescription medications without consulting a prescriber	Percentage of heartburn free 24-hour days during 14-days of randomized treatment. Measures of efficacy were reported by subjects in a daily self-assessment diary[a]	Efficacy
Secondary	**Secondary**	
To determine the proportion of subjects reporting heartburn 2 days or less during the 14-day randomized treatment period (both Weeks 1 and 2 between V3 and V4)	Proportion of subjects reporting heartburn 2 days or less during the 14-days randomized treatment period (both weeks 1 and 2 between V3 and V4)	Efficacy
To determine the efficacy of esomeprazole 20 mg qd during Days 1 to 4 of a 14-day regimen for the treatment of frequent heartburn in subjects who are likely to self-treat with non-prescription medications without consulting a prescriber	Comparison of proportion of subjects with 0, 1, 2, 3, or 4 days with no heartburn over Days 1 to 4 between esomeprazole 20 mg and placebo (the first 4 consecutive days subjects were on randomized treatment, between V3 and V4)	Efficacy
To determine the proportion of subjects with resolution of frequent heartburn for the final week, first week, and second week of the treatment phase of the study	Proportion of subjects with heartburn 1 day or less during the final week, second week, first week of treatment; Final week = the last 7 consecutive days subjects were on randomized IP (between V3 and V4)[b] Second week = second 7 consecutive days subjects were on randomized IP (between V3 and V4; Days 8 through 14) First week = the first 7 consecutive days subjects were on randomized IP (between V3 and V4; Days 1 through 7)	Efficacy

[a] Measures of efficacy were assessed by data recorded by subjects in an Interactive voice response system (IVRS) daily self-assessment diary.

[b] Indicator of frequent heartburn (FreqHB) resolution calculated as: If reporting heartburn during the week is 1 day or less during the final week/first week or second week of the randomized treatment phase, then the FreqHB resolution indicator was set equal to 1, if otherwise it was set to zero.

CSP Clinical Study Protocol; qd once daily "quaque die"; V3 Visit 3; V4 Visit 4.

Study design

This was a Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group study to determine the efficacy of esomeprazole 20 mg once daily (qd) over a 14-day regimen for the treatment of frequent heartburn in subjects who are likely to self-treat with non-prescription medications without consulting a prescriber and without a confirmed gastroesophageal reflux disease (GERD) diagnosis.

Target subject population and sample size

The target population was male and female subjects ≥18 years of age with frequent heartburn occurring ≥2 days per week. The subjects were consumers of medication for heartburn but without a confirmed GERD diagnosis. Subjects had discontinued the antacids, H_2-receptor antagonists (H_2RAs), and/or proton-pump inhibitors (PPI) treatment prior to the start of the placebo run-in period.

A total of 120 evaluable subjects per treatment group were considered to provide 95% power at an alpha level=0.05 (2-sided). In order to account for the combined effect of early discontinuation and missing data, 150 subjects per group were planned to be randomized into the study.

Investigational product and comparators: dosage, mode of administration and batch numbers

Blinded doses of oral esomeprazole 20 mg capsules (batch number 09-004156AZ) and matching placebo capsules (batch number 09-004155AZ) were taken qd orally by the subjects.

All subjects received Gelusil®[1] tablets as a rescue medication. Subjects were instructed to chew 1 tablet for heartburn symptoms as needed and repeated hourly if symptoms returned.

Duration of treatment

The duration of subject participation was 6 weeks including a 2-week (±2 days) screening/washout period, 1-week run-in period, 2-week randomization treatment period, and 1-week follow-up period. During the 1-week run-in period and 1-week follow-up period, the subjects were treated only with placebo.

Statistical methods

The full analysis set (FAS): The FAS included data from all randomized subjects who took at least 1 dose of randomized treatment and had a valid baseline heartburn assessment and at

[1] Gelusil® (aluminum hydroxide, magnesium hydroxide and simethicone) is a registered trademark, the property of WellSpring Pharmaceutical Corporation.

least 1 valid post-baseline heartburn assessment. Subjects were classified according to randomized treatment. This analysis set was used for all efficacy analyses.

The per–protocol (PP) analysis set: The PP analysis set was a subset of the full analysis set excluding data from subjects with important protocol deviations (determined by study team prior to unblinding of the data). Subjects were classified according to actual treatment received. This analysis set was used to examine the robustness of FAS results for the primary variable.

Safety analysis set: The safety analysis set included all randomized subjects who took at least 1 dose of IP.

The primary variable ie, percentage of heartburn free 24-hour days over 14-days treatment was analyzed on both the FAS and PP analysis sets. All statistical tests were 2-sided with a significance level of 5%, ie, α=0.05. Model-based point estimates were presented together with their 95% confidence intervals (CI).

A sensitivity analysis was performed where subject missing data were assumed to be days with heartburn. Safety variables were analyzed on the safety analysis set and summarized using descriptive statistics.

Subject population

Subject disposition is summarized in Table S2. In total 526 subjects were enrolled, of whom 341 subjects were randomized (170 and 171 subjects in esomeprazole 20 mg and placebo groups, respectively). Of the 170 subjects randomized to the esomeprazole 20 mg group, 165 (97.1%) received esomeprazole 20 mg. Of the 171 subjects randomized to the placebo group, 161 (94.2%) received placebo.

The mean age was 41.6 years and 42.8 years for esomeprazole 20 mg and placebo groups, respectively. The number of female subjects randomized into the study were comparable to the males subjects (86 [53.1%] versus 76 [46.9%] for esomeprazole 20 mg group and 82 [51.9%] versus 76 [48.1%] for placebo group, respectively). The majority of the subjects were White (107 [66%] and 111 [70.3%] in the esomeprazole 20 mg and the placebo groups respectively) or Black/African American (48 [29.6%] and 46 [29.1%] in the esomeprazole 20 mg and placebo groups, respectively). The percentage of days with heartburn during the run-in period was 78% in the esomeprazole 20 mg group and 79% in the placebo group.

The subjects included in the study, adults with frequent heartburn occurring ≥2 days per week and without a confirmed GERD diagnosis, were representative of the target population. The treatment groups were well balanced with regard to disposition, demographic, and disease characteristics.

Table S2 Subject disposition

	Number (%) of subjects		
	Esomeprazole 20 mg	**Placebo**	**Total**
Subjects Enrolled[a]			526
Subjects Who Were Not Randomized			185 (35.2)
Withdrawn From Study Due To Adverse Event			3 (1.6)
Withdrawn From Study Due To Death			1 (0.5)
Withdrawn From Study Due To Eligibility Criteria Not Fulfilled			181 (97.8)
Subjects Randomized	170	171	341 (64.8)
Subjects Who Received Treatment	165 (97.1)	161 (94.2)	326 (95.6)
Subjects Who Did Not Receive Treatment	5 (2.9)	10 (5.8)	15 (4.4)
Withdrawn From Study Due To Eligibility Criteria Not Fulfilled	0 (0.0)	1 (0.6)	1 (0.3)
Withdrawn From Study Due To Severe Non-Compliance To Protocol	2 (1.2)	2 (1.2)	4 (1.2)
Withdrawn From Study Due To Subject Decision	1 (0.6)	1 (0.6)	2 (0.6)
Withdrawn From Study Due To Other	2 (1.2)	6 (3.5)	8 (2.3)
Subjects Who Completed Study	151 (88.8)	152 (88.9)	303 (88.9)
Subjects Who Discontinued Study	19 (11.2)	19 (11.1)	38 (11.1)
Subject Decision	3 (1.8)	2 (1.2)	5 (1.5)
Eligibility criteria not fulfilled	0 (0.0)	1 (0.6)	1 (0.3)
Adverse event	1 (0.6)	0 (0.0)	1 (0.3)
Severe non-compliance to protocol	8 (4.7)	5 (2.9)	13 (3.8)
Development of study-specific withdrawal criteria	1 (0.6)	1 (0.6)	2 (0.6)
Other	6 (3.5)	10 (5.8)	16 (4.7)

[a] All subjects who provided informed consent.

Summary of efficacy results

Primary variable

The comparison of percentage of heartburn free 24-hour days during 14-days of treatment between esomeprazole 20 mg and placebo groups is presented in Table S3. The percentage of heartburn free 24-hour days over 14-days of randomized treatment period was statistically significantly higher in subjects receiving esomeprazole 20 mg (48.00%) as compared to placebo (32.75%). The least square (LS) mean difference between the treatment groups was 15.25% (95% CI 9.88 to 20.62; $p<0.0001$).

Table S3 Comparison of percentage of heartburn free 24-hour days during 14-days of treatment by ANCOVA between Esomeprazole 20 mg and Placebo - (Full analysis set)

	Esomeprazole 20 mg (N=162) LS Mean (SE)		Placebo (N=158) LS Mean (SE)		Difference between groups a		
Variable	**n**		**n**		**LS Mean (SE)**	**95% CI**	**p-value**
Percentage heartburn free 24-hour day	162	48.00(1.96)	158	32.75(1.99)	15.25(2.73)	(9.88,20.62)	<0.0001

[a] Obtained from analysis of covariance with centers and treatment as fixed effects and frequency of heartburn during the run-in phase as a covariate.
Missing values for the treatment phase were handled as stated in the protocol, ie, values are imputed based on the run-in phase data.
ANCOVA Analysis of covariance; CI Confidence interval; LS Least square; SE Standard error.
n– number of subjects included in the analysis.

The results of the PP analysis and sensitivity analysis, using the same method, were consistent with the primary analysis (p<0.0001).

Secondary variable

The proportion of subjects with resolution of frequent heartburn (defined as ≤2 days with heartburn) during 14-days treatment period was statistically significantly higher in subjects receiving esomeprazole 20 mg (16.67%) compared to placebo (1.27%) (RR=13.17; 95% CI 3.18 to 54.44; p<0.0001).

There was a statistically significant difference between the esomeprazole 20 mg and placebo groups in the proportion of subjects who experienced heartburn free 24-hour days in the first 4 days of treatment (OR 2.54; 95% CI 1.66 to 3.88; p<0.0001). In the placebo group 47 (29.75%) of the subjects experienced 2 or more heartburn free days during the first 4 days of treatment compared to 75 (46.30%) in the group treated with esomeprazole 20 mg.

There was a statistically significant difference in the proportion of subjects who experienced resolution of frequent heartburn in the last 7 calendar days, second week, and first 7 calendar days of the treatment period of the study between the esomeprazole 20 mg (24.69%, 23.46%, 19.75%) and placebo (10.76%, 8.23%, 4.43%) treatment groups.

The results of the secondary variables supported the outcome of the primary variable.

Summary of safety results

A summary of adverse events (AEs) in each category reported during the study is presented in Table S4. Median exposure was 14-days for both esomeprazole 20 mg and placebo groups.

Numerically there was a higher number of subjects that experienced at least 1 AE in the esomeprazole group than in the placebo group during the randomized treatment period

(25 [15.15%] versus 16 [9.94%] subjects). Overall, the events reported were isolated incidences spread across different system organ classes (SOCs) and no specific pattern was identified. This numerical difference did not raise any safety concerns.

Table S4 Number (%) of subjects who had at least 1 AE in any category in treatment period (Safety analysis set)

	Number (%) of Subjects[a]	
AE category	Esomeprazole 20 mg (N=165)	Placebo (N=161)
Any AE	25 (15.15)	16 (9.94)
Any AE with outcome = death	0 (0.00)	0 (0.00)
Any SAE (including events with outcome = death)	0 (0.00)	0 (0.00)
Any AE leading to discontinuation of treatment	1 (0.61)	0 (0.00)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category were counted once in each of those categories.
AE Adverse event; SAE Serious adverse event.

During randomized treatment period, the most commonly reported AEs by subjects who received esomeprazole 20 mg were: constipation, hemoglobin decreased, and blood glucose decreased (1.2% of subjects each). The most commonly reported AEs by subjects who received placebo were: blood glucose increased, dry mouth, nausea and pain (1.2% of subjects each). The most commonly reported AEs during esomeprazole 20 mg treatment were in the SOC of Investigations (5.45% subjects) during the randomized treatment period. The most common AEs in the placebo group were in the SOC of Gastrointestinal disorders (4.35% subjects) during the randomized treatment period.

There were no fatal AEs or SAEs reported during the randomized treatment period and there were no events qualifying as 'other significant event' for this study. One (0.61%) subject discontinued IP due to an AE (sinusitis) while on esomeprazole 20 mg.

There were no clinically relevant changes in mean values over time with regard to laboratory parameters and vital signs in either treatment group.

Esomeprazole 20 mg qd over a 14-day regimen was generally well tolerated in subjects with frequent heartburn. The safety pattern was consistent with the known safety profile of esomeprazole and no safety concerns were raised.