AstraZeneca

Clinical Study Report

Drug substance:	esomeprazole magnesium
Document No.:	GI.000-014-535
Edition No.:	D5
Study code:	D9612L00122
Date:	12 December 2008

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy Study Comparing 4 Weeks of Treatment with Esomeprazole 20 mg qd to Placebo qd in Patients with Heartburn and Sleep Disturbances Associated with Gastroesophageal Reflux Disease (GERD)

Study dates: First patient enrolled: 10 April 2008
Last patient completed: 07 July 2008

Phase of development: IV

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

Drug product:	NEXIUM®	**SYNOPSIS**	
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International co-ordinating investigator

Not applicable.

Study center(s)

This study was conducted in the United States (50 centers).

Publications

None to date.

Study dates

First patient enrolled 10 April 2008

Last patient completed 07 July 2008

Phase of development

Therapeutic use (IV)

Objectives

The primary objective of this study was to demonstrate a difference in the relief of nighttime heartburn between esomeprazole 20 mg once daily (qd) (E20) and placebo qd (placebo) after 4 weeks of treatment in patients with GERD as measured by a daily diary card.

The secondary objectives of this study were the following:

1. To assess the impact of treatment with E20 versus placebo on sleep disturbances associated with GERD, as measured by:

   – Change in global Pittsburgh Sleep Quality Index (PSQI) scores;

- Complete resolution of sleep disturbances;
- Relief of sleep disturbances;
- Percent of days without sleep disturbances;
- Time to first relief of sleep disturbances;
- Time to first resolution of sleep disturbances;
- Time to first complete resolution of sleep disturbances.

2. To assess the impact of treatment with E20 versus placebo on heartburn, as measured by:

   - Complete resolution of daytime, nighttime and 24-hour heartburn;
   - Relief of daytime and 24-hour heartburn;
   - Percent of patients with symptom improvement.

3. To assess the impact of sleep disturbances associated with GERD on work productivity and regular daily activities using the Work Productivity and Activity Impairment Questionnaire: Sleep Disturbance-GERD (WPAI-SLEEP-GERD) at Baseline and after 4 weeks of treatment, as measured by:

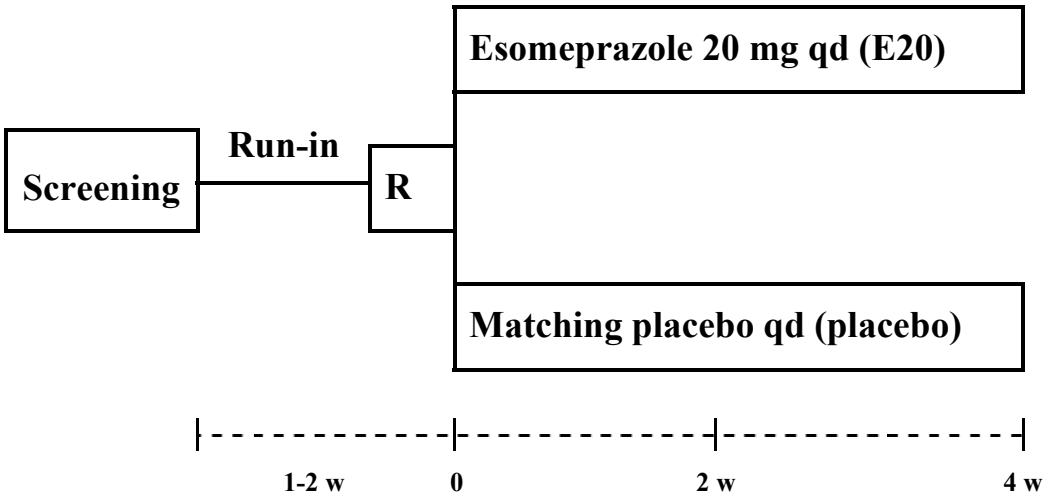
   - Percent work time missed because of sleep disturbances;
   - Percent impairment while working because of sleep disturbances;
   - Percent overall work impairment because of sleep disturbances;
   - Percent activity impairment because of sleep disturbances;
   - Monetary value of work hours saved per patient at Week 4.

4. To assess the safety and tolerability of E20 through 4 weeks of treatment.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled study.

Study Flow Chart



Screening comprised informed consent and screening.
Run-in: duration 1-2 weeks; no study treatment except rescue medication (GELUSIL®); daily diary
R is randomization.

Target patient population and sample size

This study was conducted in male and female patients, 18 to 85 years of age, and included 276 patients with GERD. At Screening, the investigator established any past history of erosive esophagitis (EE) or of episodes of heartburn or acid regurgitation for 3 months or longer. No endoscopy was done for inclusion in this study so it was expected that the study population would include symptomatic GERD (sGERD) patients with and without erosions. The patient's nighttime symptoms were to average at least 2 or 3 episodes in a 7-day period in order to be a candidate for the run-in phase. Furthermore, the patient should have had at least a 1-month history of sleep disturbances associated with GERD.

Once the investigator determined that the patient had a history of heartburn or acid regurgitation for 3 months or longer (or any history of EE), nighttime heartburn averaging at least 2 or 3 times per week, and associated sleep disturbances, the patient was entered into the run-in phase of the study. During the run-in, the patient filled out a diary card documenting both heartburn symptoms and sleep disturbances associated with GERD. To be eligible for randomization, the patient must have had both sleep disturbances associated with GERD on at least 3 of the last 7 nights of the run-in period and nighttime heartburn graded as moderate or severe on at least 3 of the last 7 nights of the same run-in period. Sleep disturbances associated with GERD could have included, but were not limited to, trouble falling asleep, unwanted awakenings, or overall poor sleep quality.

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

Drug	Dosage	Mode of Administration	Batch Number
esomeprazole magnesium	20 mg once daily	oral	H 1189-04-01
matching placebo	once daily	oral	H 0459-06-03

Duration of treatment

Four weeks of once daily (morning) dosing.

Criteria for evaluation (main variables)

Efficacy

The following efficacy endpoints were based on the patient's daily diary responses, the PSQI, and/or the WPAI-SLEEP-GERD:

Primary variable: Relief of nighttime heartburn on patient's last 7 days in the study. Relief was defined as a daily diary card response of "none" on at least 6 of 7 days, allowing for 1 "mild" response.

Secondary variables: The secondary outcome variables are presented in the following list.

1. Endpoints for sleep disturbances associated with GERD:

   - Change in global PSQI scores from Baseline to Week 4.
   - Achievement of (yes/no) developer-defined good sleep (global PSQI score ≤5) at Week 4.
   - Complete resolution of sleep disturbances associated with GERD after 1, 2, and 4 weeks of treatment, and on the patient's last 7 days in the study. Complete resolution of GERD-related sleep disturbances was defined as "No" on 7 consecutive days.
   - Relief of sleep disturbances associated with GERD after 1, 2, and 4 weeks of treatment, and on the patient's last 7 days in the study. Relief of sleep disturbances associated with GERD was defined as a daily diary response of "Yes" on not more than 2 of 7 consecutive days.
   - Percentage of days without GERD-related sleep disturbances during the 4-week treatment period.

- Days to first relief of sleep disturbances associated with GERD during the 4-week treatment period.

- Days to first resolution of sleep disturbances associated with GERD during the 4-week treatment period.

- Days to first complete resolution of sleep disturbances associated with GERD during the 4-week treatment period.

2. Endpoints for heartburn:

   - Complete resolution of daytime, nighttime, and 24-hour heartburn after 1, 2, and 4 weeks of treatment and on the patient's last 7 days in the study.

   - Relief of daytime and 24-hour heartburn after 1, 2, and 4 weeks of treatment and on the patient's last 7 days in the study. Relief was defined as a daily diary response of "none" on at least 6 of 7 days, allowing for 1 "mild" response.

   - Percentage of patients with symptom improvement based on weekly symptom score from Baseline (mean weekly score of 2-week Baseline period) compared to last week of study drug treatment. Improvement is defined as any decrease in weekly symptom score from Baseline.

3. Endpoints for WPAI-SLEEP-GERD:

   - Percent work time missed because of sleep disturbances due to GERD symptoms.

   - Percent impairment while working because of sleep disturbances due to GERD symptoms.

   - Percent overall work impairment because of sleep disturbances due to GERD symptoms.

   - Percent activity impairment because of sleep disturbances due to GERD symptoms.

   - Monetary value of work hours saved per patient at Week 4.

Safety

Another secondary objective of this study was to assess the safety and tolerability of E20 through 4 weeks of treatment. Safety and tolerability assessments included physical examination, review of adverse events, clinical laboratory evaluations, and vital sign measurements.

Statistical methods

The primary efficacy analysis was performed on a modified intention-to-treat (MITT) population as defined in the Protocol and the Statistical Analysis Plan. Patients were considered to be evaluable and were included in the MITT efficacy analysis as long as they met all of the following conditions:

1. Patient took at least 1 dose of study medication and had post-treatment data.

2. Patient had a reported history of heartburn and reported nighttime heartburn graded as moderate or severe on at least 3 out of any consecutive 7 days of the run-in period.

3. Prior to Randomization, the patient had sleep disturbances associated with GERD as documented in the run-in diary on at least 3 of the last 7 days of the run-in period.

The per protocol (PP) population included all patients from the MITT population who met a prospectively defined set of evaluability criteria according to a blinded review completed by United BioSource Corporation (UBC) prior to unblinding the study data. The safety population included all patients who took at least 1 dose of study drug and for whom post-randomization data existed.

The primary endpoint (percentage of patients in the MITT population who exhibited relief of nighttime heartburn, as measured by the diary on the patient's last 7 days in the study) was analyzed using a chi-square statistic to assess differences in the relief rates for the E20 treatment group compared to placebo.

Prior to the study, it was estimated that a sample size of 120 patients per treatment group would provide at least 90% power to detect a 20% difference in relief rates, assuming a 40% relief rate for the E20 treatment group and a 20% relief rate for the placebo treatment group. This assumed a 2-sided test at an alpha level of 0.05 using a chi-squared test for proportions. The assumed relief rates were based on heartburn results from a prior esomeprazole study (data on file for Study D961AC00001; Johnson et al., 2005).

Adverse events, laboratory test values, and vital sign values are presented descriptively. No inferential statistical methods were used for the safety data.

Patient population

In total, 431 patients were screened and 276 patients were randomized to study treatment. A large number of screen failures were anticipated due to the inclusion/exclusion criteria; therefore, it was planned to screen over 310 patients in order to enroll approximately 240 evaluable patients. Three patient populations were analyzed: MITT, PP, and the safety population. The randomized population was used for the summarization of adverse events. Characteristics of the overall study population are summarized in Table S1. Demographic characteristics of the treatment groups were comparable.

Table S1 Patient population and disposition

Disposition		E20 n	E20 (%)	Placebo n	Placebo (%)	Total n	Total (%)
Randomized		143	(100.0)	133	(100.0)	276	(100.0)
Completed protocol		138	(96.5)	124	(93.2)	262	(94.9)
Withdrawals		5	(3.5)	9	(6.8)	14	(5.1)
Evaluable for Safety [a]		142	(99.3)	132	(99.2)	274	(99.3)
Evaluable for MITT		137	(95.8)	125	(94.0)	262	(94.9)
Evaluable for PP		134	(93.7)	122	(91.7)	256	(92.8)
Demographic characteristics (MITT population)							
N		137		125		262	
Gender, n (%)	Male	48	(35.0)	40	(32.0)	88	(33.6)
	Female	89	(65.0)	85	(68.0)	174	(66.4)
Age, years	Mean (SD)	47.0	(11.7)	46.8	(12.9)	46.9	(12.3)
	Median	48.0		48.0		48.0	
	Range	21.0 to 76.0		22.0 to 79.0		21.0 to 79.0	
Race, n (%)	White	105	(76.6)	104	(83.2)	209	(79.8)
	Black/African-American	25	(18.2)	13	(10.4)	38	(14.5)
	Asian	3	(2.2)	2	(1.6)	5	(1.9)
	Native Hawaiian/ Pacific Islander	1	(0.7)	1	(0.8)	2	(0.8)
	Other	3	(2.2)	5	(4.0)	8	(3.1)
BMI (kg/m^2)	Mean (SD)	30.3	(6.9)	30.9	(7.4)	30.6	(7.1)
	Median	30.2		29.8		30.1	
	Range	17.3 to 65.6		18.3 to 63.1		17.3 to 65.6	

a Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.
BMI is body mass index; E20 is esomeprazole 20 mg; P is placebo; MITT is modified intention-to-treat (population); n is number; PP is Per protocol (population).

Efficacy results

The primary variable in this study was the percentage of patients with relief of nighttime heartburn during the last 7 days in the study. Relief was defined as a daily diary card response of "none" on at least 6 of 7 days, allowing for 1 "mild" response. Relief was analyzed in the MITT and PP populations.

For both the MITT and PP populations, the proportion of patients with relief of nighttime heartburn was significantly higher ($p < 0.0001$) in the esomeprazole treatment group versus the placebo treatment group (Table S2).

Table S2 Number and percentage of patients with relief of nighttime heartburn in last 7 days on study (MITT and PP populations)

	E20		Placebo		Differences (p-value*)
Population	**n/N**	**(%)**	**n/N**	**(%)**	**E20 vs. P**
MITT	47 / 137	(34.3)	13 / 125	(10.4)	<0.0001
PP	47 / 134	(35.1)	13 / 122	(10.7)	<0.0001

E20 is esomeprazole 20 mg; P is placebo; MITT is modified intention-to-treat population; PP is Per protocol population.
* Chi-square test

Secondary variables assessed the impact of esomeprazole treatment on sleep disturbances associated with GERD and on heartburn.

The E20 dose was effective in reducing sleep disturbances associated with GERD. A significant treatment effect in favor of E20 versus placebo was shown for complete resolution and relief of GERD-related sleep disturbances in both the MITT and PP populations. In addition, the mean percentage of days without GERD-related sleep disturbances was significantly greater for E20 versus placebo in both the MITT and PP populations. Based on analysis of global PSQI scores, E20 was significantly more effective than placebo in improving sleep quality; however, percentages of patients who had developer-defined good sleep at Week 4 but not at Baseline were not significantly different for the study treatments.

E20 was effective in reducing heartburn. A significant treatment effect in favor of E20 versus placebo was shown for complete resolution and relief of daytime, nighttime, and 24-hour heartburn after 1, 2, and 4 weeks of treatment in both the MITT and PP populations.

Health Economics variables assessed the affect of esomeprazole treatment on work productivity reduced by sleep disturbances associated with GERD. Work productivity, as measured by WPAI scores, was improved by E20. E20 was significantly more effective than placebo in reducing the equivalent number of work hours lost due to reduced productivity, the degree that sleep disturbance affected productivity, and the degree that sleep disturbance affected regular (nonwork) activity. The numbers of hours absent from work were lower for E20 treatment than for placebo treatment, but the difference was not significant. An estimate of monetary value of work hours saved (which incorporated a measure of equivalent hours saved due to increased productivity) showed a significant difference between treatment groups of USD123.60/patient at Week 4 in favor of E20.

Safety results

The E20 esomeprazole dose was well tolerated. In the E20 treatment group, a higher percentage of patients (21.0%) experienced an adverse event (AE) than in the placebo treatment group (18.2%); this pattern was also observed for treatment-related AEs. One patient in the placebo treatment group had 1 serious adverse event (SAE), which was deemed

unrelated to study drug by the Principal Investigator. There were no deaths and no other significant adverse events (OAEs) (Table S3).

The majority of the most common AEs reported were in the gastrointestinal system (Table S4). In general, these AEs were similar in frequency across treatment groups, except for some that were more frequent in the E20 group: nausea (E20 3.5%, placebo 0.8%), headache (E20 2.8%, placebo 0.8%), , diarrhea (E20 2.1%, placebo 0.0%), and vomiting (E20 2.1%, placebo 0.0%).

Table S3 Number (%) of patients who had an adverse event in any category (all randomized patients)

	Number (%) of patients who had an adverse event in each category [a]			
	E20 (N=143)		Placebo (N=133)	
Category of adverse event	**n**	**(%)**	**n**	**(%)**
Any adverse events	30	(21.0)	24	(18.2)
Serious adverse events	0	(0.0)	1	(0.8)
Treatment-related adverse events	9	(6.3)	4	(3.0)
Adverse events leading to withdrawal	1	(0.7)	1 [c]	(0.8)
Deaths	0	(0.0)	0	(0.0)
	Total number of adverse events [b]			
Any adverse events	39		31	
Serious adverse events	0		1	
Treatment-related adverse events	10		5	
Adverse events leading to withdrawal	1		1 [c]	

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
b Events are counted by preferred term, i.e., for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.
c Patient No. E0034025 reported an AE for which the action taken was reported as "permanently stopped;" however, disposition data indicated that the patient completed the study.
E20 is esomeprazole 20 mg.

Table S4 Number (%) of patients with the most common adverse events (frequency ≥1% in either treatment group) by preferred term sorted in decreasing order of frequency as summarized over all treatment groups (all randomized patients)

Adverse event (preferred term)	E20 (N=143)		Placebo (N=133)	
	n	(%)	n	(%)
Nausea	5	(3.5)	1	(0.8)
Headache	4	(2.8)	1	(0.8)
Diarrhoea	3	(2.1)	0	(0.0)
Vomiting	3	(2.1)	0	(0.0)
Back pain	2	(1.4)	1	(0.8)
Abdominal pain	1	(0.7)	2	(1.5)
Flatulence	1	(0.7)	2	(1.5)
Oedema peripheral	2	(1.4)	0	(0.0)
Sinusitis	2	(1.4)	0	(0.0)
Nasopharyngitis	0	(0.0)	2	(1.5)
Pneumonia	0	(0.0)	2	(1.5)

E20 is esomeprazole 20 mg.

Date of the report

12 December 2008