AstraZeneca

Clinical Study Report	
Drug Substance	Esomeprazole magnesium
Study Code	D9614C00096
Edition Number	
Date	23 September 2008

A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Treatment-withdrawal Study to Evaluate the Efficacy and Safety of Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Infants Aged 1 to 11 Months, Inclusive

Study dates: First patient enrolled: 12 April 2007
Last patient completed: 4 June 2008

Phase of development: III

This study was performed in compliance with Good Clinical Practice.

Drug Product	NEXIUM®	**SYNOPSIS**	
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A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Treatment-withdrawal Study to Evaluate the Efficacy and Safety of Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Infants Aged 1 to 11 Months, Inclusive

Study centre(s)

This study was conducted at a total of 33 sites in the US (16 sites), France (4 sites), Germany (9 sites), and Poland (4 sites).

Publications

None as of the completion date of this report.

Study dates		**Phase of development**
First patient enrolled	12 April 2007	Therapeutic confirmatory (III)
Last patient completed	4 June 2008	

Objectives

Primary:

The primary objective of this study was to evaluate the efficacy of once daily esomeprazole for reducing the esophageal and supraesophageal signs and symptoms of infantile gastroesophageal reflux disease (GERD).

Secondary:

The secondary objective of this study was to evaluate the safety and tolerability of once daily esomeprazole in infants aged 1 to 11 months, inclusive, with GERD.

Exploratory:

On an exploratory basis, the study described the burden of pediatric GERD on the primary caregiver from a psychological, social, and economic perspective.

Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, treatment-withdrawal study. Patients who demonstrated response to treatment in the open-label phase were eligible to enter the randomized, treatment-withdrawal phase.

Target patient population and sample size

The patient population for this study was infants aged 1 to 11 months, inclusive, with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD documented according to medically accepted standards. All patients were symptomatic at study entry. Patients were either term or post-term infants beyond the neonatal period, but less than 12 months of age, or were preterm infants with a corrected gestational age of at least 44 weeks, but less than 12 months.

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

Esomeprazole magnesium capsules were administered orally, once daily. A placebo control was used in the double-blind, randomized, treatment-withdrawal phase of the study for patients who were randomized to receive placebo.

Open-label phase: Patients were given doses according to their body weight at enrollment into the open-label treatment period (Visit 2).

Body weight	Daily dose
3-5 kg	2.5 mg
>5 kg-7.5 kg	5 mg
>7.5 kg-12 kg	10 mg

Double-blind phase: Patients were randomized in a 1:1 ratio to receive either their original (open-label phase) dose of esomeprazole or placebo. Batch numbers for each investigational product are as follows:

Esomeprazole gastro-resistant capsules 5 mg – batch number H 1504-01-03-01

Esomeprazole gastro-resistant capsules 10 mg – batch number H 1221-03-06-01

Esomeprazole gastro-resistant capsules 5 and 10 mg placebo – batch number H 1688-02-01-01

Esomeprazole gastro-resistant capsules 2.5 mg placebo – batch number H 1687-02-01-01

Excipient granules for oral suspension, aluminium sachet containing 1g granules - batch number H 1878-01-01-01

Duration of treatment

The study had a 2-week, open-label phase and a 4-week, double-blind phase.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: time from randomization to discontinuation due to symptom worsening in the randomized treatment-withdrawal phase.

- Secondary variables:

  - time from randomization to discontinuation due to any reason in the randomized treatment-withdrawal phase.

  - the proportion of treatment responders randomized into the double-blind phase that were classified as treatment successes at the end of the 4-week, double-blind phase of the study. Patients were classified as treatment successes if they maintained improvement in their symptoms throughout the double-blind phase without reaching a threshold for discontinuation or discontinuing from the study for any reason.

  - daily patient symptom assessment as reported by the parent/guardian.

  - symptom severity recorded on a Physician's Global Assessment.

Patient Reported Outcomes (PROs)

This study described the burden of pediatric GERD on the primary caregiver from a psychological, social, and economic perspective. Caregivers of all patients completed the Pediatric GERD Caregiver Impact Questionnaire (PGCIQ). The data collected from the PGCIQ will be analyzed in a separate report.

Health economics

A descriptive evaluation of the economic burden of pediatric GERD on the primary caregiver was undertaken using the PGCIQ (refer to PRO above). The data collected from the PGCIQ will be analyzed in a separate report.

Safety

Safety variables included adverse events (AEs), clinical laboratory evaluations (haematology, clinical chemistry, and urinalysis), vital signs, and physical examination.

Statistical methods

The intent-to treat (ITT) population was the primary analysis population. For summaries and formal statistical analyses conducted on data from the double-blind, treatment-withdrawal

phase of the study, the ITT analysis set included all randomized patients with available data for a particular endpoint and who took at least 1 dose of the study medication in the double-blind phase. For summaries of data collected from the open-label phase, the ITT population included all patients who were enrolled in the open-label phase who had available data for a particular endpoint and took at least 1 dose of study medication in the open-label phase.

A per-protocol analysis was not conducted because the treatment-withdrawal design of the study, with the initial open-label phase, precludes the possibility of a truly blinded assessment of violations and deviations. The relatively small sample size (80 randomized patients) also make the interpretation of such an analysis more difficult, since unless there are a large number of deviations or violations, in which case a per-protocol analysis would be under-powered, the population will not differ substantially from the that of the ITT.

Patients who were given at least 1 dose of the study medication were included in the safety analysis.

The primary endpoint of time from randomization to discontinuation due to symptom worsening during the double-blind phase of the study was analyzed using the Cox proportional hazards model, adjusting for treatment. The same approach was used to analyze time from randomization to discontinuation due to any reason. The proportion of treatment successes at the end of the double-blind phase was compared among treatment groups using a Chi-square test. Cochran-Mantel-Haenszel tests (stratifying by the assessment at randomization) were used to assess treatment differences in the end-of-study Physician's Global Assessment. The presence and severity of symptoms reported daily by the parent/guardian of the patient were summarized descriptively in the open-label and double-blind phases of the study.

Patient population

A total of 98 patients were included in the open-label phase of the study, and 80 patients were randomized to the double-blind phase of the study. The safety and ITT populations consisted of all 98 enrolled patients in the open-label phase and all 80 randomized patients in the double-blind phase. No PP analysis was performed for this study. The disposition of patients during the study is shown in Table S1.

Table S1 Patient disposition

Disposition	N (%) of patients in each category		
		Double-blind randomized treatment[a]	
	Open-label[b]	Esomeprazole	Placebo
Enrolled/randomized			
Enrolled in the open-label phase	98 (100.0)		
Evaluable for safety and ITT in the open-label phase	98 (100.0)		

Randomized in the double-blind phase	80 (81.6)	39 (100.0)	41 (100.0)
Evaluable for safety and ITT in the double-blind phase	80 (81.6)	39 (100.0)	41 (100.0)
Completed the study	0	29 (74.4)	24 (58.5)
Discontinued	18 (18.4)	10 (25.6)	17 (41.5)
Adverse event	5 (5.1)	2 (5.1)	0
Lack of therapeutic response	9 (9.2)	8 (20.5)	17 (41.5)
Voluntary discontinuation by the parent/guardian	4 (4.1)	0	0

[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] All patients received open-label esomeprazole during the open-label phase.
Data derived from Table 11.1.4, Section 11.

Eighteen (18.4%) patients discontinued during or at the end of the open-label phase. The most common reason for discontinuing the study during the open-label phase was lack of therapeutic response (9 [9.2%] patients).

Numerically more patients who were given esomeprazole (74.4%) completed the double-blind treatment period compared with those who were given placebo (58.5%). The most common reason for premature discontinuation during the double-blind phase was lack of therapeutic response (8 [20.5%] patients in the esomeprazole group and 17 [41.5%] patients in the placebo group). Two (5.1%) patients in the esomeprazole group discontinued during the double-blind randomized phase due to adverse events.

Demographic and baseline characteristics are presented in Table S2.

Table S2 Demographics and baseline characteristics (ITT population)

Characteristic	**Category**			
			Double-blind randomized treatment	
	Open-label[a]	**All randomized**	**Esomeprazole**	**Placebo**
	(n=98)	**(n=80)**	**(n=39)**	**(n=41)**
Demographics				
Sex [n (%)]				
Male	63 (64.3)	57 (71.3)	30 (76.9)	27 (65.9)
Female	35 (35.7)	23 (28.8)	9 (23.1)	14 (34.1)
Age (months)				
Mean (SD)	4.8 (2.9)	4.9 (2.9)	4.9 (2.6)	4.9 (3.2)
Median	4	4	4	3

Characteristic	Category			
			Double-blind randomized treatment	
	Open-label[a]	All randomized	Esomeprazole	Placebo
	(n=98)	(n=80)	(n=39)	(n=41)
Range	1 to 11	1 to 11	1 to 11	1 to 11
Race [n (%)]				
Caucasian	86 (87.8)	72 (90.0)	35 (89.7)	37 (90.2)
Black	4 (4.1)	2 (2.5)	2 (5.1)	0
Asian	3 (3.1)	2 (2.5)	1 (2.6)	1 (2.4)
Other	5 (5.1)	4 (5.0)	1 (2.6)	3 (7.3)
Baseline characteristics				
Weight (kg)				
Mean (SD)	6.6 (1.5)	6.8 (1.5)	6.9 (1.6)	6.7 (1.4)
Median	7	7	7	7
Range	3 to 11	4 to 11	4 to 11	4 to 10
Weight group (kg)				
3 to 5 kg	11 (11.2)	8 (10.0)	3 (7.7)	5 (12.2)
>5 kg to 7.5 kg	61 (62.2)	48 (60.0)	26 (66.7)	22 (53.7)
>7.5 kg	26 (26.5)	24 (30.0)	10 (25.6)	14 (34.1)
Height (cm)				
Mean (SD)	64.2 (5.8)	64.6 (5.7)	64.6 (5.4)	64.5 (6.0)
Median	64	64	64	64
Range	49 to 75	49 to 75	57 to 75	49 to 74
BMI (kg/m^2)				
Mean (SD)	16.0 (1.9)	16.2 (1.9)	16.4 (1.9)	16.0 (1.9)
Median	16	16	16	16
Range	11 to 22	11 to 22	12 to 22	11 to 20
Head circumference (cm)				
n	97	79	39	40
Mean (SD)	42.1 (2.7)	42.4 (2.6)	42.5 (2.6)	42.2 (2.7)
Median	42	42	42	42
Range	35 to 49	37 to 49	39 to 48	37 to 49
Dose/body weight (mg/kg)[b]				
Mean	0.88	0.89	0.86	0.92
Range	0.50 to 1.33	0.50 to 1.33	0.51 to 1.28	0.50 to 1.33

[a] All patients received open-label esomeprazole during the open-label phase.
[b] Dose in mg/kg at the start of the open-label treatment period (visit 2) when all patients were to receive open-label esomeprazole.
ITT Intent to treat; SD Standard deviation.
Data derived from Table 11.1.2.1 Section 11.

In this study, there were more males than females enrolled in both treatment phases. Most patients were Caucasian, with fewer than 12% who were non-Caucasian. The mean age of patients was approximately 4.9 months (range 1 to 11 months). The study population was distributed across the 1 to 11 month ages. Only 20 patients (20.4%) had endoscopies performed at baseline, of which only 6 patients (4 eventually randomized to esomeprazole, and 2 randomized to placebo) had erosive esophagitis.

Overall, the study population was appropriate to evaluate the safety and clinical outcomes of esomeprazole treatment for GERD in pediatric patients ages 1 to 11 months, inclusive.

Efficacy results

A numerically longer time from randomization to discontinuation due to symptom worsening was found for esomeprazole, compared with placebo, during the double-blind phase; however, the difference was not statistically significant (hazard ratio, esomeprazole/placebo: 0.69, 95% CI 0.35 to 1.35, p=0.2751). Kaplan-Meier curves by treatment, displaying the percentage of patients event-free over time, showed that numeric differences between the treatment groups appeared to emerge during the first 2-weeks of the double-blind period, with the Kaplan-Meier curves remaining relatively parallel thereafter.

Results for the secondary analysis of time to discontinuation due to any cause were identical to those of the primary analysis with numerical, but not statistically significant, differences seen, since the 2 patients who discontinued due to AEs (both randomized to double-blind esomeprazole) also had worsening of GERD symptoms as assessed by the PGA at the discontinuation assessment.

More patients who were randomized to esomeprazole were considered treatment successes at the end of the study compared with those randomized to placebo, but the difference was not statistically significant (p=0.3524).

Symptom data, as reported by the parent, showed numeric improvement in GERD symptom severity in the vomiting/regurgitation, and irritability and feeding difficulties symptom classes, but not in the supraesophageal/respiratory symptoms class, in the open-label phase. No clear differences between treatment groups were noted in any symptom class during the double-blind phase.

The majority of patients showed improvement in their GERD symptoms, as assessed by the Physician's Global Assessment, following treatment with open-label esomeprazole. However, there were no clear differences between treatment groups in the subsequent double-blind phase of the study.

Safety results

It is important to note that all dosed patients in this study received open-label esomeprazole treatment, including those patients randomized to placebo in the subsequent treatment withdrawal phase.

There were no deaths in this study. Seven patients had SAEs during the study, none of which were considered related to study treatment: 2 patients who discontinued in the open-label phase (failure to thrive; rotavirus infection), 4 patients who were given double-blind esomeprazole (respiratory syncytial virus bronchiolitis, bronchospasm, and poor peripheral circulation; gastroenteritis [this event started before entering the open-label phase]; apnea; and clamydial infection [2 events in the same patient]), and 1 patient who was given double-blind placebo (urinary tract infection [this event began during the open-label phase]). Seven patients had DAEs during the study, none of which were considered related to study treatment: 5 patients who discontinued in the open-label phase (abdominal pain; otitis media and sinusitis; failure to thrive; rotavirus infection; respiratory syncytial virus infection), and 2 patients who were given double-blind esomeprazole (abdominal pain and vomiting; gastroenteritis).

Four patients had treatment-related AEs (abdominal pain; regurgitation; tachypnea; and ALT increased). Each of the treatment-related AEs had an onset date during the open-label treatment period, when all patients received open-label esomeprazole at either the 2.5 mg or 5 mg open-label dose.

Overall, the most common AEs reported were consistent with the natural history of health and disease-related events in this pediatric age group.

There were no clinically important findings and trends in hematology, clinical chemistry, urinalysis, vital signs, or physical examination (including medical history) observed with esomeprazole.

In general, no new safety signals were identified in this population of 1- to 11-month-old pediatric patients.

Date of the report

23 September 2008