AstraZeneca

Clinical Study Report

Drug substance:	Esomeprazole magnesium
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Study code:	D9614C00097
Date:	22 May 2006

A Phase III, Multicentre, Randomized, Double-blind Parallel-group Study to Evaluate the Safety and Clinical Outcome of Once Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Pediatric Patients 1 to 11 Years of Age, Inclusive

Study dates:	First patient enrolled: 13 October 2004 Last patient completed: 09 November 2005
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, Multicentre, Randomized, Double-blind Parallel-group Study to Evaluate the Safety and Clinical Outcome of Once Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Pediatric Patients 1 to 11 Years of Age, Inclusive

International co-ordinating investigator

Not applicable.

Study centre(s)

24 study centers in Belgium, France, Italy, and the United States (US).

Publications

None.

Study dates		**Phase of development**
First patient enrolled	13 October 2004	Therapeutic confirmatory (III)
Last patient completed	09 November 2005	

Objectives

Primary: to evaluate the safety of once daily treatment with esomeprazole in relieving GERD-associated symptoms in pediatric patients 1 to 11 years of age, inclusive.

Secondary: to evaluate the clinical outcome of once daily treatment with esomeprazole in relieving GERD-associated signs and symptoms in pediatric patients 1 to 11 years of age, inclusive.

Exploratory: to describe the burden of pediatric GERD in children ages 1 to 5 years of age, inclusive on the parent/guardian from a psychological, social, and economic perspective.

Study design

This is a multicenter, parallel-group study to evaluate the safety and clinical outcome of esomeprazole treatment in patients with GERD. Patients were stratified based on weight and were randomized in a double-blind 1:1 ratio to receive either of the following:

- if weight was <20 kg, once daily treatment with esomeprazole 5 mg or 10 mg
- if weight was ≥20 kg, once daily treatment with esomeprazole 10 mg or 20 mg

Target patient population and sample size

Pediatric patients of both sexes, ages 1 to 11 years, inclusive with endoscopically proven GERD were enrolled in this study. Patients were to have an endoscopy during the screening period. Patients with a previous (within 2 weeks prior to Visit 1) diagnosis of EE by endoscopy and who were candidates for PPI therapy were not required to have an additional endoscopy at baseline (Visit 1). The established endoscopic evidence was accepted only if there was adequate documentation (ie, complete endoscopic reports, photo documentation). Patients with extraesophageal and/or atypical symptoms (ie, failure to thrive, reactive airway disease, etc.) who were candidates for endoscopy qualified for inclusion provided they had endoscopic signs of GERD.

The target was to randomize at least 50 patients 1 to 5 years of age and at least 50 patients 6 to 11 years of age to allow for a minimum of 40 patients to complete the study in each age group. Enrollment was approached in this way to ensure that esomeprazole exposure would be assessed in the full age range of children 1 to 11 years, inclusive, and that younger or older children would not dominate the population.

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

Esomeprazole magnesium blinded, blue clinical image capsules were used in this study. Patients were dosed orally according to the randomization schedule (see Study design). Dosages, formulation number, and batch numbers are summarized in Table S1. No comparator was used.

Table S1 Summary of investigational product

Investigational product	Dosage form and strength	Formulation number	Manufacture lot number
esomeprazole magnesium	capsules, 5 mg	H 1504-01-01	H 1504-01-01-03
esomeprazole magnesium	capsules, 10 mg	H 1221-02-01	H 1221-02-01-06 H 1221-02-01-08
esomeprazole magnesium	capsules, 20 mg	H 1189-04-01	H 1189-04-01-07 H 1189-04-01-08

For patients who could not tolerate swallowing capsules, parents/guardians were instructed to empty the pellet contents of the capsule into 1-2 tablespoons of applesauce.

Duration of treatment

8 weeks.

Criteria for evaluation (main variables)

Safety: (primary) changes from baseline in medical history, physical examination (including vital signs), clinical laboratory evaluations, and adverse events (AEs).

Efficacy: (secondary)

- changes from baseline in daily patient symptom assessment as reported by parent/guardian.
- changes from baseline in Physician's Global Assessment.
- changes from baseline in endoscopic healing of erosive esophagitis.

Patient Reported Outcomes: (exploratory) A descriptive evaluation of the burden of pediatric GERD on the parent/guardian was undertaken. Caregivers of patients ≤5 years of age completed the Pediatric GERD Caregiver Impact Questionnaire (PGCIQ).

Health Economics: (exploratory) The economic impact of pediatric GERD on the parent/guardian was evaluated using the PGCIQ (for patients ≤5 years of age), which collected information regarding the impact on work absenteeism, productivity on the job, and expenses for the care of the child. (Note: It was predetermined that the analysis of economic impact would be made in a separate report and not included in the Clinical Study Report.)

Statistical methods

There were 3 populations analyzed: Intent-to-treat (ITT) population, Per-protocol (PP) population, and Safety population. The ITT population included patients who had a baseline measurement, at least 1 post-baseline measurement after randomization, and who took at least 1 dose of study medication. The PP analysis was performed in support of the ITT analysis. Patients in the PP population were those who completed the study meeting all criteria of the ITT population and who did not have a major protocol violation or deviation. The Safety population included all patients who took at least 1 dose of study medication and had at least 1 post-baseline safety data value.

For the safety outcomes, data from vital signs, physical examinations, clinical laboratory tests, and AEs were collected at screening and during the treatment phase of the study. Descriptive statistics were provided to summarize the above information. No inferential statistical comparisons were planned, but exploratory statistical techniques were to be employed to aid in the investigation of unexpected safety signals or concerns as warranted. Descriptive statistics were provided for all the efficacy outcomes. Frequency tables of the Physician's

Global Assessment at baseline and for each of the on-treatment visits were constructed for each dosing group. Baseline results were then compared to each of the on-treatment results using a chi-square test. The weekly mean scores from the patient diaries (completed while on treatment by the parent/guardian) were evaluated against the baseline 72-hours symptom recall using a paired t-test for each week.

Patient population

Table S2 presents information on the demographics and disposition of patients included in this study. In total, 109 patients were randomized in 24 study sites. Of these, 101 patients completed the study. The numbers of evaluable patients were 108 patients in the safety population, 109 in the ITT population, and 98 patients in the PP population.

The age distributions (by years of age) within each dose group are presented in Table S2. In addition, the numbers of children in overall age categories of 1 to 5 years and 6 to 11 years are presented. As expected, these 2 age classifications closely approximated the 2 weight strata (Table S2), with most 1 to 5 year olds weighing <20 kg and most 6 to 11 year olds weighing ≥20 kg.

The numbers and percentages of patients with erosive and nonerosive esophagitis were evenly distributed across the treatment groups. In the total study population, 48.6% of patients had erosive esophagitis. Of the 53 patients who had erosive disease, all but 2 had LA grade A or B. One patient (4.3%) in the <20 kg, 10 mg treatment group had Grade C esophagitis and 1 patient (3.4%) in the ≥20 kg, 20 mg treatment group had Grade D.

Table S2 Patient population and disposition

	Esomeprazole dose groups				
	5 mg Wt <20 kg	**10 mg Wt <20 kg**	**10 mg Wt ≥20 kg**	**20 mg Wt ≥20 kg**	**Total**
N Randomized	26	23	31	29	109
Demographics					
Gender [n (%)]					
Male	12 (46.2)	9 (39.1)	17 (54.8)	18 (62.1)	56 (51.4)
Female	14 (53.8)	14 (60.9)	14 (45.2)	11 (37.9)	53 (48.6)
Age in years [n (%)]					
1	12 (46.2)	8 (34.8)	0	0	20 (18.3)
2	6 (23.1)	5 (21.7)	0	0	11 (10.1)
3	4 (15.4)	4 (17.4)	0	0	8 (7.3)
4	2 (7.70)	3 (13.0)	1 (3.2)	2 (6.9)	8 (7.3)
5	1 (3.8)	2 (8.7)	1 (3.2)	1 (3.4)	5 (4.6)
6	1 (3.8)	1 (4.3)	2 (6.5)	0	4 (3.7)
7	0	0	5 (16.1)	3 (10.3)	8 (7.3)
8	0	0	5 (16.1)	9 (31.0)	14 (12.8)
9	0	0	8 (25.8)	6 (20.7)	14 (12.8)
10	0	0	3 (9.7)	6 (20.7)	9 (8.3)
11	0	0	6 (19.4)	2 (6.9)	8 (7.3)
Age category [n (%)]					
1 to 5 years	25 (96.2)	22 (95.7)	2 (6.5)	3 (10.3)	52 (47.7)
6 to 11 years	1 (3.8)	1 (4.3)	29 (93.5)	26 (89.7)	57 (52.3)
Race [n (%)]					
Caucasian	19 (73.1)	19 (82.6)	26 (83.9)	25 (86.2)	89 (81.7)
Black	7 (26.9)	4 (17.4)	5 (16.1)	3 (10.3)	19 (17.4)
Other	0	0	0	1 (3.4)	1 (0.9)
Baseline characteristics					
Weight (kg)	N=26	N=23	N=31	N=28	N=108
Mean (SD)	12.8 (3.1)	14.1 (2.8)	35.5 (11.7)	34.5 (11.6)	25.2 (13.9)
Median	13	14	37	31	22
Range	8-18	10-18	20-58	21-60	8-60
Height (cm)	N=26	N=23	N=31	N=28	N=108
Mean (SD)	90.0 (11.1)	94.2 (11.7)	134.5 (13.7)	134.5 (11.2)	115.2 (24.4)
Median	89	92	135	133	118
Range	70-109	80-119	108-168	112-159	70-168
BMI (kg/m^2)	N=26	N=23	N=31	N=28	N=108
Mean (SD)	15.7 (2.1)	15.9 (1.7)	19.3 (4.8)	18.6 (3.9)	17.5 (3.8)
Median	15	16	18	17	17
Range	12-20	13-19	14-32	14-29	12-32
Dose/body weight (mg/kg)					
Mean	0.4	0.7	0.3	0.6	0.5
Range	0.3-0.6	0.6-1.0	0.2-0.5	0.3-1.0	0.2-1.0

Table S2 Patient population and disposition

	Esomeprazole dose groups				
	5 mg Wt <20 kg	**10 mg Wt <20 kg**	**10 mg Wt ≥20 kg**	**20 mg Wt ≥20 kg**	**Total**
N Randomized	26	23	31	29	109
Biopsy urease test *(H. pylori*)					
Negative	16 (61.5)	12 (52.2)	8 (25.8)	10 (34.5)	46 (42.2)
Positive	0	1 (4.3)	0	0	1 (0.9)
Unknown	10 (38.5)	10 (43.5)	23 (74.2)	19 (65.5)	62 (56.9)
Erosive disease [n (%)]	12 (46.2)	12 (52.2)	16 (51.6)	13 (44.8)	53 (48.6)
LA Grade A[a]	6 (23.1)	6 (26.1)	11 (35.5)	9 (31.0)	32 (29.4)
LA Grade B[a]	6 (23.1)	5 (21.7)	5 (16.1)	3 (10.3)	19 (17.4)
LA Grade C[a]	0	1 (4.3)	0	0	1 (0.9)
LA Grade D[a]	0	0	0	1 (3.4)	1 (0.9)
Disposition					
N (%) of completed patients	24 (92.3)	22 (95.7)	26 (83.9)	29 (100.0)	101 (92.7)
N (%) of discontinued patients	2 (7.7)	1 (4.3)	5 (16.1)	0	8 (7.3)
N (%) analyzed for safety	25[b] (96.2)	23 (100.0)	31 (100.0)	29 (100.0)	108 (99.1)
N (%) analyzed for efficacy (ITT)	26 (100.0)	23 (100.0)	31 (100.0)	29 (100.0)	109 (100.0)
N (%) analyzed for efficacy (PP)	25 (96.2)	22 (95.7)	26 (83.9)	25 (86.2)	98 (89.9)

Wt is weight; N is number; ITT is Intention-to-treat; PP is Per-protocol.

[a] Erosive disease LA score classification: Grade A is 1 (or more) mucosal break no longer than 5 mm that does not extend between the tops of 2 mucosal folds; Grade B is 1 (or more) mucosal break more than 5 mm that does not extend between the tops of 2 mucosal folds; Grade C is 1 (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but which involves less than 75% of the circumference; D is 1 (or more) mucosal break that involves at least 75% of the circumference.

[b] One patient was not evaluable for safety because he did not have any post-baseline safety data. Some post-baseline diary (clinical outcomes) data was available for this patient so he was included in the ITT population.

Safety results

Table S3 summarizes adverse events (AEs) by category. There were no deaths in this study. There were 3 serious adverse events (SAEs) of which 2 occurred during or after treatment with esomeprazole. The other SAE occurred during the Screening endoscopy, prior to randomization; therefore, this SAE is not included in Table S3. None of the SAEs were considered treatment related by the investigator. There were 4 discontinuations due to adverse events (DAEs), 1 of which was also an SAE. Three of the 4 DAE patients had AEs that were considered not treatment-related. One DAE patient had AEs considered as possibly treatment-related (asthenia, nausea, viral infection) and these resolved within 1 day of onset.

As observed in Table S3, a total of 13 treatment-related AEs was reported in 10 patients (9.3%, 10/108 patients). The incidences of these were equally distributed amongst the 2 weight strata, 5 patients in the <20 kg stratum and 5 in the ≥20 kg stratum.

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]									
	Esomeprazole dose groups									
	5 mg Wt <20 kg (N=25)		10 mg Wt <20 kg (N=23)		10 mg Wt ≥20 kg (N=31)		20 mg Wt ≥20 kg (N=29)		Total (N=108)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any adverse events	17	(68.0)	15	(65.2)	26	(83.9)	24	(82.8)	82	(75.9)
Serious adverse events (SAEs)	0		1	(4.3)	1	(3.2)	0		2[b]	(1.9)
SAEs leading to death	0		0		0		0		0	
SAEs not leading to death	0		1	(4.3)	1	(3.2)	0		2	(1.9)
Treatment-related adverse event	4	(16.0)	1	(4.3)	4	(12.9)	1	(3.4)	10	(9.3)
Discontinuations of study treatment due to adverse events	0		1	(4.3)	3[c]	(9.7)	0		4	(3.7)
Other significant adverse event	0		0		0		0		0	
	Total number of adverse events									
Any adverse events (AEs)	57		61		102		91		311	
Treatment-related AEs	5		1		6		1		13	

Wt is weight; SAE is serious adverse event; AE is adverse event.

[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] Patient E0030012 had an SAE during the Screening endoscopy and before randomization into the study. Because this patient had not yet received study medication, the SAE is not counted in this table.

[c] Patient E00420009 is included in the DAE count in this table because the Investigator had marked on the AE CRF page that the AE contributed to study termination. The AE was not primary reason for discontinuation. Primary reason for withdrawal (recorded on CRF termination page) was "lack of therapeutic response."

From Table S3, it is observed that the frequencies of adverse events were approximately 20% higher in the ≥20 kg treatment groups than in the <20 kg treatment groups. This is possibly due to the fact that the mean age of patients in the ≥20 kg treatment groups was 8.4 years old, while the mean age of patients in the <20 kg treatment group was 2.3 years old. There are many differences between these 2 age populations, such as school attendance, daily environment, developmental abilities, etc. These differences may have affected the AE reporting. Although a difference was observed in the frequencies of overall AE reports, the frequencies of treatment-related AEs were similar across the 2 weight strata.

Table S4 summarizes the most commonly reported AEs, regardless of causality assigned by the investigator. AE occurrences did not appear to be dose related. Overall, the most common AEs reported were consistent with the natural history of health and disease-related events in this pediatric age group. No new safety signals were identified in this population of 1 to 11 year old pediatric patients. In general the AEs reported were consistent with the known safety profile of esomeprazole.

Table S4 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency (safety analysis set)—all adverse events regardless of time or causality

	Esomeprazole dose groups									
	5 mg Wt <20 kg (N=25)		10 mg Wt <20 kg (N=23)		10 mg Wt ≥20 kg (N=31)		20 mg Wt ≥20 kg (N=29)		Total (N=108)	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vomiting	5	(20.0)	2	(8.7)	6	(19.4)	7	(24.1)	20	(18.5)
Pyrexia	3	(12.0)	4	(17.4)	5	(16.1)	3	(10.3)	15	(13.9)
Diarrhoea	4	(16.0)	0		6	(19.4)	3	(10.3)	13	(12.0)
Cough	4	(16.0)	1	(4.3)	5	(16.1)	3	(10.3)	13	(12.0)
Headache	1	(4.0)	0		7	(22.6)	4	(13.8)	12	(11.1)
Nasal congestion	2	(8.0)	3	(13.0)	2	(6.5)	2	(6.9)	9	(8.3)
Lymphadenopathy	2	(8.0)	2	(8.7)	2	(6.5)	2	(6.9)	8	(7.4)
Upper respiratory tract infection	2	(8.0)	3	(13.0)	1	(3.2)	2	(6.9)	8	(7.4)
Constipation	1	(4.0)	3	(13.0)	2	(6.5)	1	(3.4)	7	(6.5)
Pharyngolaryngeal pain	1	(4.0)	1	(4.3)	4	(12.9)	1	(3.4)	7	(6.5)
Viral infection	0		0		4	(12.9)	2	(6.9)	6	(5.6)
Nasopharyngitis	3	(12.0)	0		2	(6.5)	1	(3.4)	6	(5.6)
Abdominal pain	0		1	(4.3)	3	(9.7)	1	(3.4)	5	(4.6)
Abdominal pain upper	0		1	(4.3)	2	(6.5)	2	(6.9)	5	(4.6)
Eczema	1	(4.0)	2	(8.7)	1	(3.2)	1	(3.4)	5	(4.6)
Otitis media	1	(4.0)	2	(8.7)	1	(3.2)	0		4	(3.7)
Nausea	0		0		2	(6.5)	1	(3.4)	3	(2.8)
Seasonal allergy	0		0		1	(3.2)	2	(6.9)	3	(2.8)
Sinus congestion	0		0		1	(3.2)	2	(6.9)	3	(2.8)
Tympanic membrane disorder	0		2	(8.7)	0		0		2	(1.9)
Sinusitis	0		0		0		2	(6.9)	2	(1.9)
Excoriation	0		0		2	(6.5)	0		2	(1.9)
Epistaxis	0		0		0		2	(6.9)	2	(1.9)
Teething	2	(8.0)	0		0		0		2	(1.9)
Hordeolum	2	(8.0)	0		0		0		2	(1.9)
Rhinitis	2	(8.0)	0		0		0		2	(1.9)

Wt is weight.
a Events with a total frequency of ≥5% in any treatment group are included in this table.

There were no clinically important trends within or between treatment groups with respect to hematology or clinical chemistry laboratory values. In addition, there were no clinically important findings in vital signs or physical examinations.

Efficacy results

Analysis of the Physician Global Assessments showed that overall GERD-related symptoms were reduced from baseline after treatment with all doses of esomeprazole studied. A

statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment arms ($p<0.0036$).

Analysis of the patient diary assessments (as filled out by the parent/guardian) for those patients having the GERD symptoms of heartburn, acid regurgitation, and epigastric pain at baseline showed that these symptoms were significantly reduced from baseline after treatment with esomeprazole 5 mg ($p\leq0.0005$), esomeprazole 10 mg ($p\leq0.0032$ for <20 kg patients, $p<0.0001$ for ≥20 kg patients), and esomeprazole 20 mg ($p\leq0.0002$).

Analysis of the endoscopy results for the 45 patients who had EE at baseline and had a follow-up endoscopy showed that 93.3% (42 patients) were improved from baseline. In most of these patients (88.9%), the EE was resolved and all erosions had healed. The positive results in improvement and resolution were observed across all treatment groups. While all dosing levels were associated with relief of symptoms, it was also noted that all patients whose EE was not healed had received doses in the range of 0.17 to 0.66 mg/kg.

Patient Reported Outcome (PRO) results

For the parent/guardians of children ages 1 to 5 years, inclusive, mean values for most PGCIQ dimensions suggested that a reduction (ie, improvement) had occurred in the frequency of negative issues being measured (psychological and social impact). The dimensions of the PGCIQ with the largest change were: physical health, emotional well being of the caregiver, and experiences in taking care of the child.

Date of the report

22 May 2006