AstraZeneca

Clinical Study Report

Drug substance:	Esomeprazole magnesium
Document No.:	
Edition No.:	
Study code:	D9614C00098
Date:	03 October 2005

A Phase III, Multicenter, Randomized, Double-blind, Parallel-group Study to Evaluate the Safety of Once Daily Esomeprazole for the Treatment of Clinically Diagnosed Gastroesophageal Reflux Disease (GERD) in Pediatric and Adolescent Patients 12 to 17 Years of Age, Inclusive

Study dates:	First patient enrolled: 20 February 2004 Last patient completed: 04 May 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, Multicenter, Randomized, Double-blind, Parallel-group Study to Evaluate the Safety of Once Daily Esomeprazole for the Treatment of Clinically Diagnosed Gastroesophageal Reflux Disease (GERD) in Pediatric and Adolescent Patients 12 to 17 Years, Inclusive

International co-ordinating investigator

Not applicable.

Study center(s)

In this study, 31 centers in France (3), Italy (1), Canada (7), and the United States (20) enrolled patients.

Publications

None.

Study dates		**Phase of development**
First patient enrolled	24 February 2004	Therapeutic confirmatory (III)
Last patient completed	04 May 2005	

Objectives

Primary: The primary objective of this study was to evaluate the safety and tolerability of once daily treatment with esomeprazole in pediatric and adolescent patients 12 to 17 years of age, inclusive, with clinically diagnosed GERD.

Secondary: The secondary objective of this study was to evaluate the clinical outcome of once daily treatment with esomeprazole in relieving GERD-associated signs and symptoms in pediatric and adolescent patients 12 to 17 years of age, inclusive, with clinically diagnosed GERD.

Exploratory: An additional objective of this study was to describe the burden of illness in adolescent patients with GERD as measured by a disease-specific health-related Quality of Life instrument, the QOLRAD. Additionally, this study compared the response profile of adolescent GERD patients on the QOLRAD to existing data from adult patients (Note: the comparison to adult data was not started by the Clinical Study Report completion date; therefore, results are not presented).

Study design

This study was a Phase III, multicenter, randomized, double-blind study.

Target patient population and sample size

This study was planned to enroll approximately 140 male and female pediatric and adolescent patients 12 to 17 years of age, inclusive with a clinical diagnosis of GERD to complete a minimum of 108 evaluable patients. Of the 108 evaluable patients, at least 100 patients were to be included in the range from 12 to 16 years of age, inclusive, and at least 8 patients were to be 17 years of age, inclusive.

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

Esomeprazole magnesium oral capsules—20 mg (Batch number: H1189-04-01-08) and 40 mg (Batch number: H1222-04-01-11) once daily (qd). There was no comparator in this study.

Duration of treatment

Eight weeks.

Criteria for evaluation (main variables)

Safety: (primary variable) assessment of changes from baseline in medical history, physical examinations, clinical laboratory evaluations, and adverse events.

Efficacy: (secondary variables) 1) assessment of changes from baseline in daily patient symptom assessment as reported by the patient and 2) assessment of changes from baseline in Physician Global Assessment.

Patient Reported Outcomes: (exploratory variable) A GERD-specific health related Quality of Life questionnaire, the QOLRAD, was used in this study to collect Patient-reported Outcomes (PRO) on an exploratory basis.

Statistical methods

Data from medical history, physical examinations, clinical laboratory tests, and adverse events were collected at screening and during the treatment phase of the study to assess the primary safety objective. Descriptive statistics were provided to summarize the above information. No inferential statistical comparisons were planned, but exploratory statistical techniques were employed to aid in the investigation into any unexpected safety signals or concerns as

warranted. Descriptive statistics and p-values for changes from baseline were provided for the efficacy outcomes (secondary).

Patient population

There were 149 patients randomized in this study and all were evaluable for the ITT analysis. For the safety analysis, 148 patients were evaluable as 1 patient did not have any postbaseline safety data available. For the PP analysis, 126 patients were evaluable. The distributions of all demographic characteristics were similar across the esomeprazole 20 mg and 40 mg treatment groups. Most of the patients in this study were Caucasian (83.2%) and/or female (59.7%). The weight and BMI ranges of the population were broad but the mean and median values were similar in both treatment groups. Each year of age in the 12 to 17 years range was well represented in the study population.

Table S1 Patient population and disposition

		E20		E40		Total	
Population							
N randomized		76	(100.0)	73	(100.0)	149	(100.0)
Demographic characteristics							
Sex [n, (%)]	Male	29	(38.2)	31	(42.5)	60	(40.3)
	Female	47	(61.8)	42	(57.5)	89	(59.7)
Age [n, (%)]	12 years	16	(21.1)	15	(20.5)	31	(20.8)
	13 years	11	(14.5)	13	(17.8)	24	(16.1)
	14 years	18	(23.7)	15	(20.5)	33	(22.1)
	15 years	15	(19.7)	13	(17.8)	28	(18.8)
	16 years	5	(6.6)	10	(13.7)	15	(10.1)
	17 years	11	(14.5)	7	(9.6)	18	(12.1)
Race [n, (%)]	Caucasian	62	(81.6)	62	(84.9)	124	(83.2)
	Black	8	(10.5)	7	(9.6)	15	(10.1)
	Other[a]	6	(7.9)	4	(5.5)	10	(6.7)
Disposition							
N (%) of patients who	Completed	60	(78.9)	67	(91.8)	127	(85.2)
	discontinued	16	(21.1)	6	(8.2)	22	(14.8)
N analyzed for safety[b]		75		73		148	
N analyzed for efficacy (ITT)		76		73		149	
N analyzed for efficacy (PP)		62		64		126	

[a] The classification "Other" was used when the patient had a mixed or indeterminate response.
[b] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

ITT is Intention to treat; N is Number; PP is Per-protocol; E20 is esomeprazole 20 mg qd; E40 is esomeprazole 40 mg qd.

Safety results

There were no deaths or serious adverse events in this study. In general, the occurrence of adverse events was similarly distributed across treatment groups. There were more discontinuations due to adverse events (DAEs) in the esomeprazole 20 mg treatment group than in the 40 mg group, but the overall number of DAEs in this study was low (6 patients out of 148, 4.1%) [Table S2].

Table S2 Number (%) of patients who had an adverse event in any category (safety population)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]					
	E20 (N=75)		E40 (N=73)		Total (N=148)	
Any adverse events	56	(74.7)	57	(78.1)	113	(76.4)
Serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
Serious adverse events leading to death	0	(0.0)	0	(0.0)	0	(0.0)
Serious adverse events not leading to death	0	(0.0)	0	(0.0)	0	(0.0)
Treatment-related adverse event	11	(14.7)	11	(15.1)	22	(14.9)
Discontinuations of study treatment due to adverse events	5	(6.7)	1	(1.4)	6	(4.1)
Other significant adverse event	0	(0.0)	0	(0.0)	0	(0.0)
	Total number of adverse events					
Any adverse events	165		165		330	
Treatment-related adverse events	21		17		38	

[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.

E20 is esomeprazole 20 mg qd; E40 is esomeprazole 40 mg qd.

There were a total of 38 treatment-related AEs reported in 22 patients that were equally distributed amongst the esomeprazole 20 mg and 40 mg treatment groups. The most common treatment-related AEs were headache (12/148, 8.1%), abdominal pain (4/148, 2.7%), diarrhoea (3/148, 2.0%), and nausea (3/148, 2.0%).

Table S3 summarizes all AEs (treatment-related and other) that occurred in ≥3% of the patients in either treatment group. The most common AEs reported by this population were consistent with the known safety profile of esomeprazole.

Table S3 **Number (%) of patients with the most commonly reported adverse events reported by preferred term and listed in descending order of frequency (safety population)**

Preferred Term	Treatment regimen					
	E20 (N=75)		E40 (N=73)		Total (N=148)	
	n	(%)	n	(%)	n	(%)
Headache	12	(16.0)	15	(20.5)	27	(18.2)
Abdominal pain	9	(12.0)	9	(12.3)	18	(12.2)
Nasopharyngitis	9	(12.0)	9	(12.3)	18	(12.2)
Diarrhoea	6	(8.0)	8	(11.0)	14	(9.5)
Upper respiratory tract infection	9	(12.0)	4	(5.5)	13	(8.8)
Vomiting	5	(6.7)	7	(9.6)	12	(8.1)
Cough	6	(8.0)	5	(6.8)	11	(7.4)
Nausea	6	(8.0)	4	(5.5)	10	(6.8)
Pharyngolaryngeal pain	1	(1.3)	9	(12.3)	10	(6.8)
Pyrexia	5	(6.7)	2	(2.7)	7	(4.7)
Sinusitis	3	(4.0)	4	(5.5)	7	(4.7)
Constipation	2	(2.7)	4	(5.5)	6	(4.1)
Nasal congestion	4	(5.3)	1	(1.4)	5	(3.4)
Abdominal pain upper	2	(2.7)	3	(4.1)	5	(3.4)
Abdominal tenderness	1	(1.3)	3	(4.1)	4	(2.7)
Dizziness	3	(4.0)	0	(0.0)	3	(2.0)
Dysmenorrhoea	3	(4.0)	0	(0.0)	3	(2.0)
Pain	0	(0.0)	3	(4.1)	3	(2.0)

Note: This table uses a cut-off of 3% in either treatment group for "most commonly reported adverse events." E20 is esomeprazole 20 mg qd; E40 is esomeprazole 40 mg qd.

Efficacy results

Analysis of the patient diary assessments showed that the GERD symptoms of heartburn, acid regurgitation, and epigastric pain were significantly reduced after treatment with esomeprazole 20 mg ($p<0.0001$) or esomeprazole 40 mg ($p<0.0001$) for 8 weeks.

Analysis of the Physician Global Assessments showed that overall GERD-related symptoms were reduced after treatment with either esomeprazole 20 mg or esomeprazole 40 mg. A significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) in both treatment arms ($p<0.0001$).

Patient Reported Outcome (PRO) results

Patients in both esomeprazole dose groups showed improvements in all QOLRAD domains from baseline through final visit. For patients in the esomeprazole 20 mg treatment group, the mean changes for all domains were greater than 0.5 units. For patients in the esomeprazole 40 mg treatment group, the mean changes for the emotional distress, sleep dysfunction, food/drink problems, and vitality domains were greater than 0.5 units; however, the mean change for the physical/social functioning domain was 0.4 units.

Date of the report

03 October 2005