AstraZeneca

Drug product:	Nexium	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
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A Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Effects of Esomeprazole 40 mg bid on the Signs and Symptoms of Chronic Posterior Laryngitis in Patients with Suspected Laryngopharyngeal Reflux

Study center(s)

This study was conducted at 7 centers located throughout the United States.

Publications

None.

Study dates		**Phase of development**
First patient enrolled	19 February 2002	Therapeutic exploratory (II)
Last patient completed	19 March 2003	

Objectives

The primary objective of this study was to evaluate the efficacy of acid suppression therapy at Week 16 (final visit) on symptoms associated with chronic posterior laryngitis (CPL) in patients with and without pharyngeal acid reflux (PAR).

The secondary objectives were to evaluate the efficacy of acid suppression therapy on resolution of signs of CPL at Weeks 8 and 16 (final visit) in patients with and without documented PAR at baseline; to document the quality of life score of CPL patients using a newly developed quality of life questionnaire, the CPL-HRQL; to evaluate the safety and tolerability of esomeprazole given at a dose of 40 mg twice daily (bid) for 16 weeks; to document if laryngopharyngeal reflux (LPR), as documented on 24-hour ambulatory pharyngoesophageal pH monitoring (APEM) by PAR events, is associated with the signs and symptoms of CPL.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group, 16-week, proof-of-concept study in patients with suspected LPR and CPL to evaluate the hypothesis that potent acid suppression therapy will relieve the signs and symptoms of CPL. The 16-week double-blind treatment period was preceded by a 7-day run-in period during which baseline symptoms of CPL were assessed.

Target patient population and sample size

Male and female adult patients with symptoms of throat clearing, cough, globus, sore throat, or hoarseness for at least 3 consecutive months prior to entry; who had completed at least 80% of the diary entries during the 7-day run-in period; whose cumulative primary symptom score was at least 9 over the 7-day run-in period with at least 3 days of at least Moderately Severe symptoms; and who had not used a proton pump inhibitor (PPI) during the 14 days prior to screening. Approximately 120 patients were to be randomized into this study in a 2:1 ratio (esomeprazole: placebo) to receive esomeprazole 40 mg bid or placebo bid for 16 weeks.

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

Esomeprazole delayed release capsule (40 mg) administered orally twice daily (bid), batch number H-1222-04-01-0 or placebo matching esomeprazole delayed release capsule, administered orally bid, batch number H-0459-06-03-09.

Duration of treatment

16 weeks

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Resolution of the primary symptom of CPL as assessed by the patient in the daily diary card at the Final Visit.
- The following secondary variables were evaluated in this study:
  - Proportion of patients with resolution of primary symptom at Weeks 4, 8, 12, and 16 as assessed by the patient daily diary.
  - Proportion of patients with relief of primary symptom at Weeks 4, 8, 12, 16, and the Final Visit as assessed by the patient daily diary.
  - Percentage of symptom-free days for primary symptom at Weeks 4, 8, 12, 16, and Final Visit as assessed by the patient daily diary.
  - Change in mean primary symptom score from baseline to Weeks 4, 8, 12, 16, and Final Visit.

- Proportion of symptom-free patients for the primary symptom and for each symptom separately at Weeks 4, 8, 12, 16, and Final Visit as assessed by the patient daily diary.
- Change in overall average symptom score (all symptoms) from baseline to Weeks 4, 8, 12, 16, and Final Visit.
- Proportion of symptom-free patients for each symptom at Weeks 4, 8, 12, 16, and Final Visit as assessed by investigator assessments.
- Investigator overall assessment of each CPL symptom at the Final Visit.
- Proportion of patients with resolution of all CPL signs as evaluated by laryngoscopic examination at Week 8, Week 16, and the Final Visit.
- Proportion of patients with improvement in CPL signs as evaluated by laryngoscopic examination at Week 8, Week 16, and the Final Visit.
- Change from baseline in total CPLI score at Weeks 8, 16, and Final Visit.
- Change from baseline in CPL-HRQL total score and domain score at Final Visit.
- Proportion of patients with normal or abnormal esophageal pH at baseline, as well as proportion with normal or abnormal esophageal pH as a function of primary CPL symptom.
- Number of PAR events at baseline overall and as a function of primary CPL symptom.

Safety

Number and percent of patients with adverse events, changes from baseline in clinical laboratory tests, vital signs, and ECG parameters and the incidence of abnormal laboratory values.

Statistical methods

All formal statistical tests comparing esomeprazole and placebo were performed using a 2-sided hypothesis test with a significance level of 0.050. The primary variable, resolution of the primary CPL symptom at the Final Visit, was analyzed using a logistic regression analysis that included terms for treatment and baseline symptom severity. The primary population for efficacy analyses was the ITT population.

All safety analyses were performed using the safety population. No inferential statistical method was used for the analysis of safety data, only descriptive statistics.

Patient population

A total of 146 patients were randomized in a 2:1 ratio to treatment with esomeprazole 40 mg or placebo; 1 patient assigned to the placebo group was lost to follow-up before receiving any study treatment. Thus, 145 patients received at least 1 dose of study drug and comprised the safety population, all of whom were analyzed for efficacy in the intent-to-treat (ITT) population. The 2 treatment groups were well balanced with respect to demographic and key baseline characteristics related to CPL symptomatology and laryngoscopic signs. The mean primary symptom score during the 7-day run-in period was 3.3 in both groups (ie, between Moderate and Moderately Severe), and about one-half of the patients in the esomeprazole 40 mg and placebo groups identified throat clearing as their primary symptom.

Table S1 Patient population and disposition

		Esomeprazole 40 mg		**Placebo**		**Total**	
Population							
N randomized (N planned)		95	(80)	51	(40)	146	(120)
Demographic characteristics							
Sex (n and % of patients)	Male	48	(50.5)	23	(46.0)	71	(49.0)
	Female	47	(49.5)	27	(54.0)	74	(51.0)
Age (years)	Mean (SD)	51.47	(15.15)	50.46	(14.46)	51.12	(14.87)
	Range	20.00 to 84.00		21.00 to 76.00		20.00 to 84.00	
Race (n and % of patients)	Caucasian	84	(88.4)	43	(86.0)	127	(87.6)
	Black	2	(2.1)	1	(2.0)	3	(2.1)
	Asian	1	(1.1)	3	(6.0)	4	(2.8)
	Other	8	(8.4)	3	(6.0)	11	(7.6)
Baseline characteristics							
Primary symptom score	Mean (SD)	3.3	(1.0)	3.3	(0.9)	3.3	(1.0)
Primary symptom (n and % of patients)	Throat clearing	49	(51.6)	23	(46.0)	72	(49.7)
	Hoarseness	18	(18.9)	11	(22.0)	29	(20.0)
	Cough	11	(11.6)	8	(16.0)	19	(13.1)
	Globus	8	(8.4)	5	(10.0)	13	(9.0)
	Sore throat	9	(9.5)	3	(6.0)	12	(8.3)
Disposition							
N (%) of patients who	Completed	83	(87.4%)	43	(84.3%)	126	(86.3%)
	Discontinued	12	(12.6%)	8	(15.7%)	20	(13.7%)

Table S1 Patient population and disposition

	Esomeprazole 40 mg	Placebo	Total
N analyzed for safety[a]	95	50	145
N analyzed for efficacy (ITT)	95	50	145
N analyzed for efficacy (Per Protocol)	85	48	133

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number; PP=Per-protocol

The mean number of PAR events recorded from the baseline pH monitoring study was <1.0 in both treatment groups, and only a minority of patients in either treatment group had an abnormal pH level as recorded from the distal or proximal probes. No associations were apparent between the occurrence of PAR events, or the incidence of an abnormal pH level, and the identity of the primary symptom, baseline CPLI, or baseline overall average symptom score. Baseline scores on CPL-HRQL suggested that, on average, quality of life was not seriously impacted by patients' disease, since the mean overall scale score at study entry in both treatment groups was approximately 30 on a theoretical scale of 0 to 100.

Efficacy and pharmacodynamic results

No statistically significant differences were observed between the esomeprazole 40 mg and placebo groups with respect to the primary efficacy endpoint or any of the secondary efficacy endpoints based on the patient daily diary card or investigator assessments of CPL symptoms and laryngoscopic signs. Key efficacy findings are summarized in Table S2 below.

Table S2 Key efficacy findings (ITT population)

Efficacy Variable	Esomeprazole 40 mg (N=95)		Placebo (N=50)		P-value
Primary efficacy variable					
Resolution of primary symptom at Final Visit (diary card), n (%) patients	14	(14.7)	8	(16.0)	0.799
Secondary efficacy variables					
Relief of primary symptom at Final Visit (diary card), n (%) patients	40	(42.1)	23	(46.0)	0.621
Percent symptom-free patients at Final Visit (diary card), n (%) patients	9	(9.5)	4	(8.0)	0.785
Percent of symptom-free days at Final Visit (diary card), mean (SD)	11.1	(22.49)	10.4	(21.87)	0.876
Percent symptom-free patients at Final Visit (investigator evaluations), n (%) of patients	12	(12.6)	6	(12.0)	1.000

Table S2 Key efficacy findings (ITT population)

Efficacy Variable	Esomeprazole 40 mg (N=95)		Placebo (N=50)		P-value
Change in total CPLI at Final Visit (investigator evaluations), mean (SD)[a]	-1.6	(2.13)	-2.0	(2.55)	0.446

[a] Number of patients with evaluable laryngoscopic examination data was 89 for esomeprazole and 47 for placebo.

ITT intent-to-treat; SD standard deviation

There were no statistically significant differences in the mean change from baseline to the Final Visit between the esomeprazole 40 mg and placebo groups for either the total CPL-HRQL score or any of the domain scores. Even among patients with an abnormal esophageal pH level at study entry, there was no discernable treatment-related difference in the percentage of patients with resolution of the primary symptom or improvement of larynoscopic signs at the Final Visit.

Safety results

Overall, administration of esomeprazole, 40 mg bid, for up to 16 weeks was well tolerated (Table S3). The tolerability profile for esomeprazole was comparable to that observed for placebo. No patient died, and serious adverse events and discontinuations due to adverse events occurred infrequently in both treatment groups. The expected rise in serum gastrin levels was observed following esomeprazole treatment. Neither study treatment was associated with changes in body weight, vital sign or ECG parameters, or other clinical laboratory tests. A summary of the most common (incidence of ≥5% across both treatment groups) treatment-emergent adverse events is provided in Table S4.

Table S3 Number (%) of patients who had an adverse event in any category, and total numbers of adverse events (safety population)

	Esomeprazole 40 mg (N=95)		Placebo (N=50)		Total (N=145)	
Adverse event category[a]	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
At least 1 adverse event	66	(69.5)	31	(62.0)	97	(66.9)
Drug-related adverse event	8	(8.4)	2	(4.0)	10	(6.9)
Withdrawals due to adverse event	6	(6.3)	1	(2.0)	7	(4.8)
Serious adverse event	1	(1.1)	1	(2.0)	2	(1.4)

[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.

Table S4 Number (%) of patients with most commonly reported adverse events, (safety population)

	Number (%) of patients			
MedDRA Preferred term[a]	**Esomeprazole 40 mg (N=95)**		**Placebo (N=50)**	
Upper respiratory tract infection NOS	16	(16.8%)	9	(18.0%)
Respiratory tract infection NOS	10	(10.5%)	1	(2.0%)
Diarrhea NOS	5	(5.3%)	1	(2.0%)
Nasopharyngitis	5	(5.3%)	2	(4.0%)
Medical device discomfort	4	(4.2%)	4	(8.0%)
Sinusitis NOS	3	(3.2%)	4	(8.0%)
Bronchitis NOS	1	(1.1%)	4	(8.0%)

[a] Events with a total frequency of ≥5% across both treatment groups are included in this table.
NOS not otherwise specified

Date of the report

14 May 2004