Drug product:	Nexium	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
Edition No.:	1		
Study code:	D9612L00085		
Date:	03 April 2008		

A randomised, open, phase IV, parallel group multicentre study to evaluate a change of management in Gastroesophageal Reflux Disease (GERD) patients by treatment with esomeprazole 40 mg or any other Proton Pump Inhibitor (PPI), after initial treatment failure, in ordinary clinical practice during 4 weeks.

Study centre(s)

This was a multicentre study conducted in 57 centres in Sweden.

Study dates		**Phase of development**
First patient enrolled	9 December 2005	Therapeutic use (IV)
Last patient completed	2 February 2007	

Objectives

Primary objective:

The primary objective of this study was to assess how Proton Pump Inhibitors (PPI) treated GastroEsophageal Reflux Disease (GERD) patients with insufficient symptom control would benefit from a change in management by providing a more efficient acid secretion inhibition during 4 weeks, by evaluation of esomeprazole 40 mg compared to pre-study PPI treatment.

Primary outcome variable

Proportion of patients free from heartburn

The secondary objectives in this study were:

Number of treatment failures during the study

To assess productivity with regard to symptom severity and frequency by means of the updated version of Work Productivity and Activity Impairment Questionnaire: Gastro-Esophageal Reflux Disease (WPAI-GERD) questionnaire.

To assess utility values with regard to symptom severity and frequency by means of EuroQol 5D (EQ-5D) questionnaire.

To describe which patients would benefit from a more efficient acid secretion inhibitor by means of a Quality Assurance of GERD Treatment Questionnaire (Kvalitetsuppföljning av RefluxTerapi, KURT).

To evaluate Willingness To Pay (WTP) with regard to symptom severity and frequency by assessment of WTP questions.

To assess safety by evaluation of Serious Adverse Events (SAE) and Discontinuations due to Adverse Events (DAE).

Study design

This was a randomised, open, phase IV, parallel group multicentre study to investigate how PPI treated GERD patients with insufficient symptom control would benefit from a more efficient acid secretion inhibition.

Target patient population and sample size

The study included male and female patients aged 18-65 years who, despite PPI treatment, had a history of reflux symptoms with heartburn as the predominant symptom.

The sample size calculation was based on a two group continuity corrected test with a 0.050 two-sided significance level which would have 80% power to detect the difference between one treatment with 19% patients free of heartburn and another treatment with 9% patients free of heartburn when the sample size in each group is 208 patients. With a dropout percentage of 7% 448 randomised patients were necessary in the two treatment groups together. The rather low dropout rate was expected due to the short duration of the study.

Due to an actual dropout rate of 5.7 % a lower number of patients could be randomised into the study.

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

Esomeprazole entero tablets 40 mg, once daily.

Comparator product were all other oral PPI medication labelled for the treatment of Reflux symptoms (i.e. omeprazole, pantoprazole, lansoprazole and rabeprazole tablets), used in the same administration as prior to the study but with the dosage increased within the approved dose range, at the discretion of the investigator.

Since the drugs were delivered by pharmacies on prescription, batch numbers are not available.

Duration of treatment

The treatment period was 4 weeks.

Criteria for evaluation (main variables)

Primary variable

Efficacy

- Proportion of patients free from heartburn

Secondary variables

Efficacy

- Number of treatment failures during the study period (i.e. moderate or severe heartburn persisting more than four consecutive days).

Patient reported outcomes (PROs)

- EQ-5D Questionnaire
- KURT Questionnaire

Health economic outcomes

- WPAI-GERD Questionnaire
- WTP

Safety

- SAE
- DAE

Statistical methods

The efficacy variables were analysed according to the Intention To Treat (ITT) approach in which all patients who received at least one dose of study drug after randomisation were included. For the primary efficacy variable an additional analysis according to the Per Protocol (PP) approach were performed. If the conclusions drawn from the PP analysis were similar to those drawn from the ITT analysis no further PP analyses were performed. If, however, this was not the case, all efficacy variables were to be analysed according to PP as well.

The safety analysis set included all randomised patients.

Patient population

Table S1 Patient population and disposition

		Esomeprazole		Adjusted dose		Total	
Population							
N randomised (N planned)		213	(225)	223	(225)	436	(450)
Demographic characteristics							
Sex (n and % of patients)	Male	82	(39.09)	82	(37.8)	164	(38.4)
	Female	128	(61.0)	135	(62.2)	263	(61.6)
Age (years)	Mean (SD)	49.0	(11.0)	50.3	(10.5)	49.6	(10.8)
	Range	20 – 66		24 – 65		20 - 66	
Race (n and % of patients)	Caucasian	206	(98.1)	210	(96.8)	416	(97.4)
	Black	1	(0.5)	1	(0.5)	2	(0.5)
	Oriental	3	(1.4)	5	(2.3)	8	(1.9)
	Other	-		1	(0.5)	1	(0.2)
Baseline characteristics							
Reflux symptoms during past 7 days n (%)							
	None	1	(0.5)	1	(0.5)	2	(0.5)
	Mild	45	(21.4)	46	(21.2)	91	(21.3)
	Moderate	137	(65.2)	147	(67.7)	284	(66.5)
	Severe	27	(12.9)	23	(10.6)	50	(11.7)
Number of days with symptoms							
	Mean (SD)	5.3	(1.8)	5.2	(1.9)	5.2	(1.8)
	Median	5.0		5.0		5.0	
	Range	0-7		0-7		0-7	
Disposition							
N (%) of patients who	Completed	198	(93.0)	213	(95.5)	411	(94.3)
	Discontinued	15	(7.0)	10	(4.5)	25	(5.7)
N analysed for safety[a]		213		223		436	
N analysed for efficacy (ITT)		210		217		427	
N analysed for efficacy (PP)		177		192		369	

[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

Baseline characteristics and demographics of the two treatment groups were well matched.

Efficacy results

Table S2 Number and proportion of patients free from heartburn at end-of-study, ITT

	Esomeprazole (N=210)	Adjusted dose (N=217)	Total (N=427)	
N(%) free from heartburn	132(62.9)	151(69.6)	283(66.3)	
N(%) not free from heartburn	67(31.9)	62(28.6)	129(30.2)	
Not recorded	11(5.2)	4(1.8)	15(3.5)	
Adjusted N(%) not free from heartburn	78(37.1)	66(30.4)	144(33.7)	p-value 0.1420

Note: The adjusted number of patients not free from heartburn includes patients without recordings at week 4.
SOURCE DOCUMENT: T14.SAS GENERATED: 14:44:17 03JUL2007 DB version DEV: D9612L00085

66% of the patients were free from heartburn at end-of-study. The results are numerically better in the adjusted dose group but the results are not statistically significant.

Table S3 Number and proportion of patients with treatment failures during the study, ITT

	Esomeprazole (N=210)	Adjusted dose (N=217)	Total (N=427)	
N(%) with treatment failure	12(5.7)	20(9.2)	32(7.5)	p-value 0.1699
N(%) without treatment failure	198(94.3)	197(90.8)	395(92.5)	
Not recorded	0	0	0	
Adjusted N(%) with treatment failure	12(5.7)	20(9.2)	32(7.5)	

Note: The adjusted number of with treatment failure includes patients without recordings during the study and patients with treatment failure not recorded as heartburn.
SOURCE DOCUMENT: T26.SAS GENERATED: 16:14:12 03JUL2007 DB version DEV: D9612L00085

7 % of the patients had treatment failures during the study period. There was numerically fewer treatment failures in the esomeprazole group, but the difference was not statistically significant.

EQ-5D

After four weeks treatment with more efficient acid inhibition there was a clinically significant improvement with utility values corresponding to those of a healthy population.

There was no statistically significant difference in utility between the treatment groups at end of study. However, the change from baseline to end-of-study was greater in the esomeprazole treated group.

KURT

Both treatment groups showed marked improvement. The improvement for the esomeprazole group was significantly better than for the adjusted dose group.

WPAI-GERD

Four weeks treatment with more efficient acid inhibition gives a reduction in productivity loss corresponding to a value of 1 506 SEK (2 368 – 862) per week per patient in the total population.

WTP

The value of a more efficient acid inhibitory treatment expressed by the patients as WTP was 701 SEK in the total study population. Patients who respond to treatment express a higher WTP than those not responding.

Safety results

Adverse Events (AE) in general were not recorded, only those that led to a discontinuation.

Few patients discontinued. There were slightly more discontinuations in the esomeprazole group.

There were no Overdoses or Serious Adverse Events (SAE) reported during the study.

There were no safety concerns.

Table S4 Number (%) of patients who discontinued due to an adverse event (DAE) (Safety Analysis Set)

Category of adverse event	Patients who had an adverse event in each category[a]					
	Esomeprazole (N=213)		Adjusted dose (N=223)		Total (N=436)	
Discontinuations of study treatment due to adverse events; n and(%)	10	(4.7)	5	(2.2)	15	(3.4)

Table S5 Number (%) of patients with the most commonly reported[a] adverse events leading to discontinuation, sorted by decreasing order of frequency as summarised over all treatment groups (ITT)

Adverse event (preferred term)	Esomeprazole (N=213)		Adjusted dose (N=223)		Total (N=436)	
	n	%	n	%	n	%
Nausea	3	(1.4)	1	(0.5)	4	(0.9)
Vomiting	0		2	(1.0)	2	(0.45)
Dyspepsia	1	(0.5)	1	(0.5)	2	(0.45)
Headache	2	(1.0)	0		2	(0.45)

[a] Events with a total frequency of ≥0.4% across all treatment groups are included in this table.