Drug product:	Esomeprazole, Nexium®	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
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A study to assess the effectiveness of Esomeprazole 40 mg once daily in patients with continuing Gastroesophageal Reflux Disease (GORD) symptoms following treatment with a previous full dose Proton Pump Inhibitor (PPI). An 8 week, open label, multicentre study. (RESPONSE Study)

Chief investigator

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Study centre(s)

This multicentre study was conducted at 17 General Practice centres in the UK.

Publications

None at the time of reporting

Study dates		**Phase of development**
First patient enrolled	13 September 2006	Therapeutic use (IV)
Last patient completed	18 May 2007	

Objectives

The primary objective of this study was to assess the change in the frequency of heartburn from entry to the end of the study, after 8-weeks treatment with esomeprazole 40 mg compared to previous full dose PPI treatment given once daily.

The secondary objectives of this study were to assess:

- Change in frequency of heartburn after 4 weeks treatment from baseline value at entry into the study

- Change in severity of heartburn after 4 and 8 weeks treatment from baseline value at entry into the study
- Change in severity and frequency of epigastric pain and acid regurgitation after 4 and 8 weeks treatment from baseline values at entry into the study.
- Change in symptom control on esomeprazole 40 mg from baseline to 4 and 8 weeks using the Reflux Disease Questionnaire (RDQ)
- Symptom control, defined as more symptom free days, as assessed by the GORD Impact Scale (GIS) at weeks 4 and 8.

Study design

This was a multi-centre, open label study in which patients were treated with esomeprazole 40 mg for 8 weeks. Patients attended a screening visit before initiation of study treatment and 2 further clinic visits at 4 weeks and 8 weeks.

Target patient population and sample size

The target patient population was patients diagnosed with GORD, who had been previously treated with a proton pump inhibitor (PPI) at a full dose, given once daily for a maximum period of up to 8 weeks, but were still experiencing symptoms of GORD.

The sample size was based on the change in the frequency of heartburn from baseline to 8 weeks. To detect a reduction of at least 1 day in the frequency of heartburn during the previous week, assuming a standard deviation of 2.8, at the 5% significance level and with 90% power required 85 patients. Assuming a dropout rate of 15%, it was planned to enrol approximately 100 patients in the study.

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

Esomeprazole, single 40 mg film coated tablet, was to be taken orally once daily before breakfast. Batch numbers: HC10496 for 14 x 2 blister strips GL10337 for 7 x 1 blister strip.

Duration of treatment

Eight weeks

Criteria for evaluation (main variables)

Efficacy

- Primary variable:
  - Change in frequency of heartburn after 8 weeks of esomeprazole 40 mg from baseline value at entry into the study
- Secondary variables:

- Change in frequency of heartburn after 4 weeks treatment from baseline value at entry into the study
- Change in severity of heartburn after 4 and 8 weeks treatment from baseline value at entry into the study
- Change in severity and frequency of epigastric pain and acid regurgitation after 4 and 8 weeks treatment from baseline values at entry into the study

Patient reported outcomes (PROs)

- PRO variables:
  - Change in the Reflux Disease Questionnaire (RDQ) after 4 and 8 weeks treatment from baseline value at entry into the study
  - Responses to GORD Impact Scale (GIS) questions and level of GORD control at baseline and after 4 and 8 weeks treatment

Safety

- Safety variables:
  - Nature, incidence and severity of serious adverse events (SAEs) and adverse events leading to discontinuation of a patient from study treatment (DAEs)

Statistical methods

The primary and secondary efficacy and PRO variables were analysed using a full analysis set (FAS), which comprised all patients with at least one assessment of efficacy after initiation of study treatment. The safety variables were analysed using the safety analysis set, which comprised all patients who took at least one dose of the investigational product and for whom post-dose information was available. The primary variable was also analysed using a per protocol analysis set to assess the sensitivity of the FAS results.

Primary and secondary efficacy variables: The changes from baseline to 4 and 8 weeks in the frequency and severity of the GORD symptoms of heartburn, acid regurgitation and epigastric pain were analysed by the Wilcoxon signed rank test.

Secondary PRO variables: the changes from baseline to 4 and 8 weeks in the RDQ global and dimensions scores were analysed by the Wilcoxon signed rank test. The GIS data were summarised using descriptive statistics.

Patient population

The patient population and disposition is shown in Table S1. In total, 99 patients from 17 research sites in the United Kingdom were enrolled in the study and received study treatment. Eighteen of the 99 (18.2%) patients receiving study treatment were discontinued. All 99

patients who entered the study treatment period were analysed for safety and 94 (94.9%) were analysed for efficacy and patient reported outcomes in a full analysis set.

Table S1 Patient population and disposition

		Number of patients	
Population			
Number enrolled (Number planned)		99	(100)
Number received treatment (Number planned)		99	(85)
Disposition			
Number (%) of patients who	completed	81	(81.8)
	discontinued	18	(18.2)
Analysis sets			
Number (%) analysed for safety[a]		99	(100)
Number (%) analysed for efficacy, full analysis set		94	(94.9)
Number (%) analysed for efficacy, per-protocol		86	(86.9)

[a] Number of patients who took at least one dose of the investigational product and for whom post-dose information was available.

The patient demographic and baseline characteristics are given in Table S2. The mean age of the population was 46 years and all were of Caucasian origin. If patients had not been entered into this study, the normal practice for the majority of the patients (63, 67%) would have been to be prescribed another PPI.

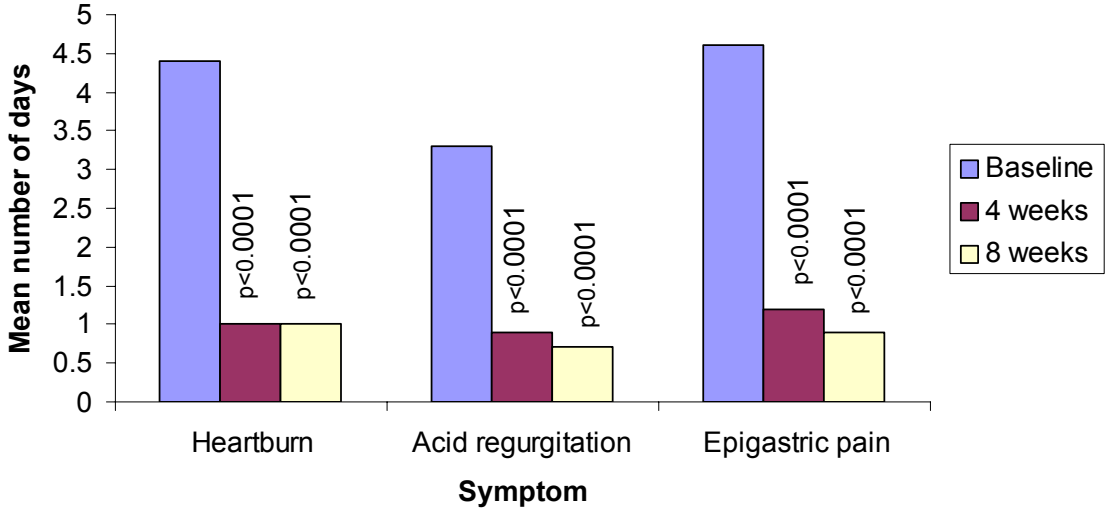
Table S2 Patient population and disposition, full analysis set

	Full analysis set (n=94)
Demographic characteristic	
Sex (n and % of patients)	
Male	37 (39.4%)
Female	57 (60.6%)
Age (years)	
Mean (SD)	46.1 (16.1)
Range	18 to 77
Race (n and % of patients)	
Caucasian	94 (100.0%)
Baseline characteristics	
History of GORD symptoms (months)	
Mean (SD)	56.1 (97.9)
Median	11.5
Duration of current episode of GORD (weeks)	
Mean (SD)	9.53 (8.78)
Frequency of heartburn in last week (days)	
Mean (SD)	4.4 (2.3)
Previous PPI (n and % of patients)	
Lansoprazole 30 mg	25 (26.6%)
Omeprazole 20 mg	67 (71.3%)
Rabeprazole 40 mg	2 (2.1%)

Efficacy results

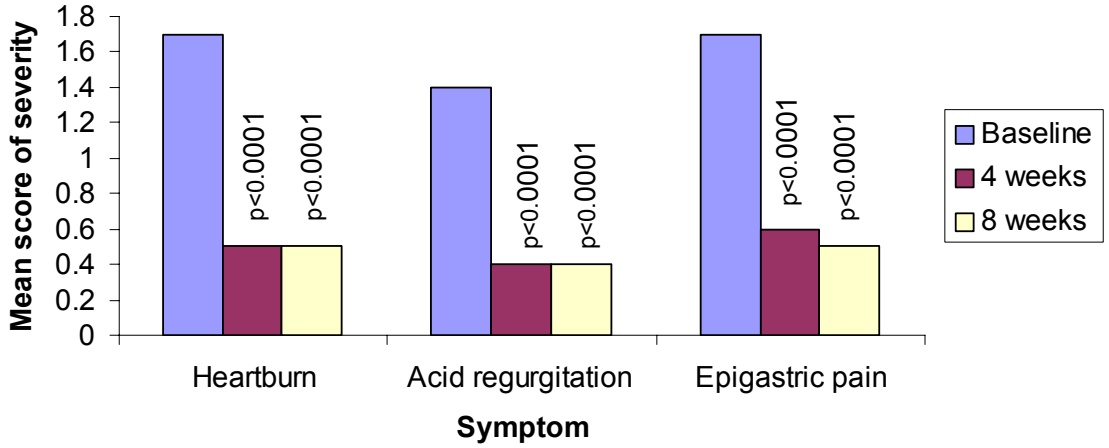
The mean frequency and severity of GORD symptoms at baseline, 4 weeks and 8 weeks are presented graphically in Figure S1 and Figure S2. The statistical analyses of the changes from baseline to 4 and 8 weeks are given in Table S3.

Figure S1 Mean frequency of symptoms at baseline and after 4 and 8 weeks of treatment



Frequency: Number of days per week

Figure S2 Mean severity of symptoms at baseline and after 4 and 8 weeks of treatment



Severity: 4-point Likert scale; 0=none, 1=mild, 2=moderate and 3=severe

Table S3 Statistical analysis of changes from baseline to 4 and 8 weeks in GORD symptoms, full analysis set

	Baseline		Change from baseline		95% CI of change	P value
	Mean	(SD)	Mean	(SD)		
4 weeks						
Frequency						
Heartburn	4.4	(2.3)	-3.4	(3.0)	(-4.0, -2.8)	<0.0001
Acid regurgitation	3.3	(2.8)	-2.4	(2.6)	(-3.0, -1.9)	<0.0001
Epigastric pain	4.6	(2.5)	-3.4	(2.7)	(-4.0, -2.9)	<0.0001
Severity						
Heartburn	1.7	(0.8)	-1.3	(1.1)	(-1.5,-1.0)	<0.0001
Acid regurgitation	1.4	(1.0)	-1.0	(1.0)	(-1.2,-0.8)	<0.0001
Epigastric pain	1.7	(0.9)	-1.1	(1.0)	(-1.4, -0.9)	<0.0001
8 weeks						
Frequency						
Heartburn	4.4	(2.3)	-3.4	(2.8)	(-4.0, -2.8)	<0.0001
Acid regurgitation	3.3	(2.7)	-2.6	(2.5)	(-3.1, -2.1)	<0.0001
Epigastric pain	4.6	(2.5)	-3.6	(3.0)	(-4.2, -3.0)	<0.0001
Severity						
Heartburn	1.7	(0.8)	-1.2	(1.1)	(-1.4, -1.0)	<0.0001
Acid regurgitation	1.4	(1.0)	-1.0	(1.0)	(-1.2, -0.8)	<0.0001
Epigastric pain	1.7	(0.9)	-1.3	(1.2)	(-1.5, -1.0)	<0.0001

Frequency: Number of days per week
Severity: 4-point Likert scale; 0=none, 1=mild, 2=moderate and 3=severe

Primary variable: Change in frequency of heartburn from baseline to 8 weeks

The mean frequency of heartburn was reduced from 4.4 days a week to 1 day a week at the end of the 8-week treatment period with esomeprazole ($p<0.0001$). This corresponds to a mean reduction of 78% in the frequency of heartburn.

Secondary variables

Other GORD symptoms (severity of heartburn, severity and frequency of acid regurgitation, and severity and frequency of epigastric pain) were also significantly reduced following 4 and 8 weeks of treatment with esomeprazole (all p<0.0001).

Control of heartburn symptoms was achieved within 4 weeks of starting treatment with esomeprazole with a mean reduction in the frequency of heartburn to 1 day a week (mean change in frequency of heartburn from baseline –3.4 days, p<0.0001). This corresponds to a mean reduction of 78% in the frequency of heartburn.

Forty-three (46%) patients who were experiencing GORD symptoms at baseline despite PPI treatment were asymptomatic (ie, had no heartburn, acid regurgitation or epigastric symptoms) after 8 weeks of esomeprazole treatment.

The frequency of heartburn in the subgroup of patients with mild heartburn on a minimum of 4 days at baseline of patients was significantly lower after 8 weeks of treatment with esomeprazole (mean change from baseline -4.6 days, p=0.0002). The severity of heartburn was reduced by a mean of 0.5, but the difference was not statistically significant in this small group of 13 patients who had mild heartburn at baseline (p=0.1094).

Both the frequency and severity of heartburn in the subgroup of patients with moderate or severe heartburn on at least 2 days at baseline were significantly reduced after 8 weeks of treatment with esomeprazole (mean changes from baseline: frequency -4.0 days, p<0.0001; severity –1.7, p<0.0001).

PRO results

Reflux Disease Questionnaire (RDQ)

Significant improvements in the RDQ global score, and heartburn, acid regurgitation, dyspepsia and GORD dimension scores of the RDQ were evident after 4 and 8 weeks of esomeprazole treatment (all p<0.0001, Table S4). Similar results were observed after 4 weeks of treatment.

Table S4 Statistical analysis of changes from baseline to 8 weeks in RDQ scores, full analysis set

Score [a]	Baseline [b]		Change from baseline		95% CI of change	P value
	Mean	SD	Mean	SD		
Global score	2.49	(0.95)	-1.81	(1.30)	(-2.08, -1.54)	<0.0001
Heartburn	2.59	(1.29)	-1.87	(1.64)	(-2.20, -1.53)	<0.0001
Acid regurgitation	2.05	(1.31)	-1.37	(1.45)	(-1.67, -1.07)	<0.0001
GORD dimension	2.32	(1.05)	-1.62	(1.34)	(-1.90, -1.35)	<0.0001
Dyspepsia	2.85	(1.26)	-2.19	(1.54)	(-2.51, -1.88)	<0.0001

[a] RDQ scores measured on a 6 point Likert scale, 0 to 5. A reduction in the score indicates an improvement in the patient's reflux disease symptoms.

[b] Baseline only presented for patients with data at both baseline and 8 weeks

GORD impact scale (GIS)

Thirty-seven percent of patients treated with esomeprazole assessed their overall level of control as 'well controlled' after 8 weeks of treatment using the GIS (Table S5).

Table S5 Number (%) of patients with level of GORD control at baseline, 4 and 8 weeks derived from responses to GIS, full analysis set

	Number (%) of patients (n=94)					
Level of control [a]	**Baseline**		**4 weeks**		**8 weeks**	
Very poorly controlled (0)	17	(18.1)	3	(3.2)	4	(4.3)
Poorly controlled (1-3)	57	(60.6)	16	(17.0)	19	(20.2)
Uncontrolled (4-5)	15	(16.0)	12	(12.8)	11	(11.7)
Fairly well controlled (6-8)	5	(5.3)	30	(31.9)	25	(26.6)
Well controlled (9)	0		30	(31.9)	35	(37.2)
Missing	0		3	(3.2)	0	

[a] Level of control was derived as the number of GIS questions with a response of 'none of the time'. The number in brackets after each category indicates the number of 'none of the time' responses applicable for that level of control.

Safety results

The mean exposure to esomeprazole 40 mg was 51 days. A summary of the SAEs and DAEs is shown in Table S6. Overall, esomeprazole was well tolerated over the 8-week treatment period. The frequency of SAEs and DAEs reported during the study was low and their nature was as expected given the patient population under study. None of the SAEs was assessed as causally related to the study drug. Diarrhoea was the only DAE or SAE reported by more than one patient (2 patients, 2%).

Table S6 Number (%) of patients who had a serious adverse event or an AE leading to discontinuation of study treatment, safety analysis set

Category of adverse event	Number (%) of patients
Serious adverse events	
Serious adverse events leading to death	0
Serious adverse events not leading to death	3 (3.0)
Discontinuations of study treatment due to adverse events (DAE)	9 (9.1)
Causally related serious adverse event	0
Causally related DAE	4 (4.0)

[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] Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 frequency of the event is counted.

Conclusion(s)

- The frequency of heartburn was reduced from baseline to the end of the 8-week treatment period with esomeprazole 40 mg for patients previously treated with full dose PPI.
- The frequency of heartburn was reduced from baseline after 4 weeks of treatment with esomeprazole 40 mg for patients previously treated with full dose PPI.
- The severity of heartburn was reduced from baseline after 4 and 8 weeks of treatment with esomeprazole 40 mg for patients previously treated with full dose PPI.
- The frequency and severity of epigastric pain and acid regurgitation were reduced from baseline after 4 and 8 weeks of treatment with esomeprazole 40 mg for patients previously treated with full dose PPI.
- The RDQ scores were reduced from baseline after 4 and 8 weeks of treatment with esomeprazole 40 mg for patients previously treated with full dose PPI.
- A higher proportion of patients were 'well controlled' after 4 and 8 weeks of treatment with esomeprazole 40 mg, compared with the patient's previous treatment with full dose PPI, as derived from responses to the GIS.
- Esomeprazole 40 mg was well tolerated over the 8-week treatment period.

Date of the report

30 August 2007