Clinical Study Report Synopsis

Drug Substance	Esomeprazole
Study Code	D9612L00116
Edition Number	2.0
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An open label, multicentre study of Nexium (esomeprazole) 40 mg once daily in subjects with symptoms of Gastroesophageal Reflux Disease (GORD) after treatment with a full dose of Proton Pump Inhibitor (PPI) – NEON

Study dates: First subject enrolled: 13 November 2007
Last subject last visit: 03 October 2008

Phase of development: Therapeutic use (IV)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Objectives and criteria for evaluation

The objectives and criteria for evaluation are given in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
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 40mg compared to previous full dose PPI treatment given once daily	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.
Secondary	**Secondary**
The secondary objectives of the study were to assess the: 1. Change in frequency of heartburn after 4-week treatment 2. Change in severity of heartburn after 4 and 8 weeks treatment 3. 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 4. Change in symptoms control on esomeprazole 40mg from baseline to 4 and 8 weeks using the Reflux Disease Questionnaire (RDQ) 5. Symptom control, defined as more symptom free days than baseline, as assessed by the GORD Impact Scale (GIS) at weeks 4 and 8 6. Safety and Tolerability of esomeprazole	1. 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. 2. 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. 3. 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 4. 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 5. 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.

Study design

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

Target subject population and sample size

The target subject population was subjects 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 4.5, at the 5% significance level and with

95% power requires 290 subjects. Assuming a dropout rate of 20%, it is planned to enrol a minimum of 325 subjects 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: IG11238 14 X 1 blister strip, 70100023 14 x 1 blister strip, IL1145114 x 1 blister strip, IM11523 14 x 1 blister strip, KA11640 14 x 1 blister strip, HL10844 7 x 1 blister strip, IC11075 7 x 1 blister strip, IH11311 7 x 1 blister strip, 7040214 7 x 1 blister strip, 8040225 7 x 1 blister strip.

Duration of treatment

Eight weeks

Statistical methods

The primary and secondary efficacy and PRO variable were analysed using a full analysis set (FAS), which comprised all subjects 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 subjects who took at least one dose of the investigational product and for whom post-dose information was available. The primary available 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 Wilcox on 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 Wilcox on signed rank test. The GIS data were summarized using descriptive statistics.

Subject population

The subject population and disposition is shown in Table S2 and Table S3. In total, 337 subjects from 20 sites in Argentina, Colombia, Chile and Venezuela were enrolled in the study. Three hundred and seventeen subjects received the study treatment. Sixteen (0.5%) subjects receiving study treatment were discontinued. All 317 subjects who entered the study treatment were analysed for safety and 311 (98.11%) were analysed for efficacy in a full analysis set.

Table S2 Study analysis sets

	Number (%) of patients
Enrolled	**337**
Received study treatment	**317**
Safety	**317 (100%)**
Full analysis set (FAS)	**311 (98.11%)**
Per protocol (PP)	**301 (94.95%)**

Percentages are based on all treated patients

Table S3 Patient disposition

	Number (%) of patients
Number of patients enrolled	337
Number of patients randomized	317 (100%)
Number (%) of patients who discontinued after randomization	16 (0.5%)
Reason for discontinuation	
Incorrect enrollment	4 (0.13%)
Voluntary Discontinuation by subject	5 (0.16%)
Subject Lost to Follow Up	7 (0.22%)
Number (%) of patients who completed the study	301 (94.95%)

Percentages calculated for each reason for discontinuation are based on the number of patients randomized

The demographic characteristics of study patients are summarized in Table S4. The overall mean age of the population was 42.7 years (18-86 years) and there were more females (68.2%) than males (31.8%). Subjects were recruited from 20 centres throughout the Latin America. The study population were of Caucasian origin (54.7%), Hispanic origin (45.0%) and Black origin (0.3%)

Table S4 Demographic characteristics

Demographic characteristic	Full analysis set (n=311)
Sex (n and % of patients)	
Male	**99 (31.83%)**
Female	**212 (68.17%)**
Age (years)	
Mean (SD)	**42.7 (14,27)**
Range	**18 to 86**
Race (n and % of patients)	
Caucasian	**170 (54,66%)**
Hispanic	**140 (45,02)**
Black	**1 (0,32 %)**

The subject population had a history of GORD symptoms ranging from 0.47 month to 36.5 years with a median of 24.33 months. The median duration of current episode was 5 weeks with a range from 0.43 to 77.14 weeks.

The majority of subjects (92.6%) had experienced at least mild heartburn in the previous week.

The baseline characteristics are given in Table Table S5.

Table S5 Baseline characteristics

Baseline GORD characteristic	Full analysis set (n=311)
History of GORD symptoms (months)	
Mean (SD)	**38,41 (53,07)**
Median	**24,33**
Range	**0,47 to 438**
Duration of current episode of GORD (weeks)	
Mean (SD)	**9,15 (10,28)**
Median	**5.00**
Range	**0.43 to 77.14**
Frequency of heartburn in last week (days)	
Mean (SD)	**3,9 (2.25)**
Median	**4.0**
Range	**0 to 7**
Severity of heartburn in last week, n (%)	
None	**23 (7,4%)**
Mild	**75 (24.12%)**
Moderate	**143 (45,98%)**
Severe	**70 (22,51%)**

Summary of 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 analysis of the changes from baseline to 4 and 8 weeks are given in Table S6.

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

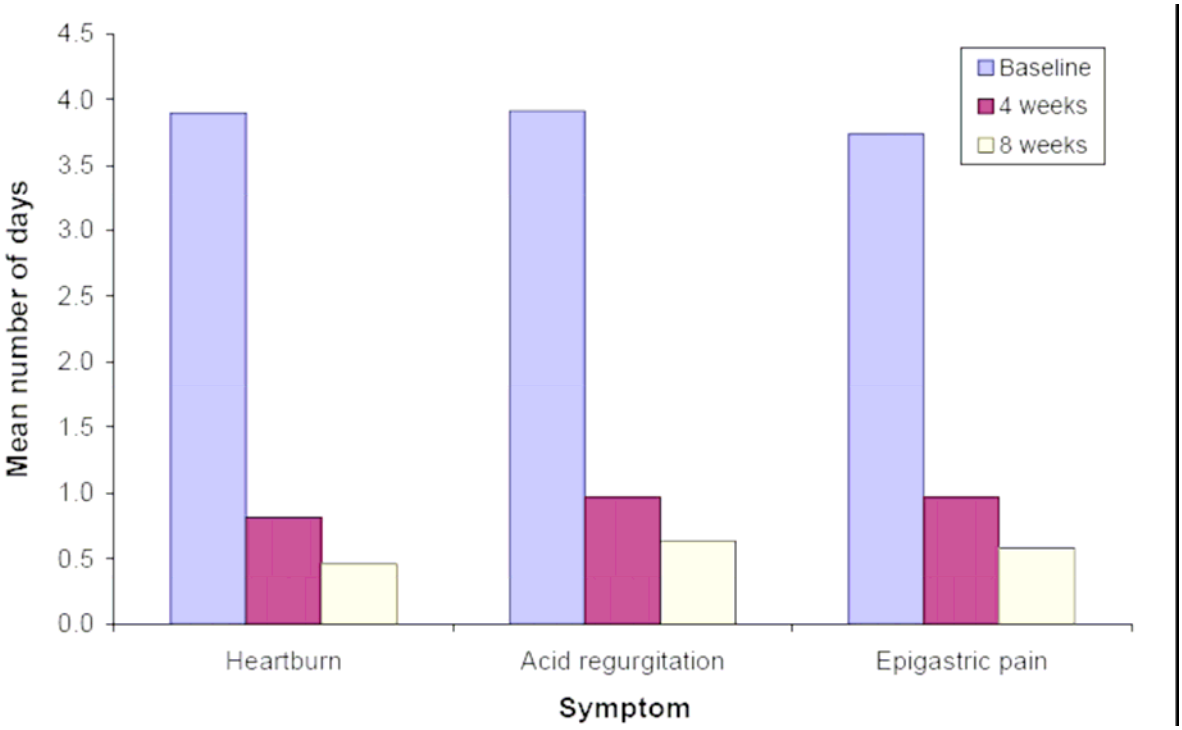

Figure S2 **Mean Severity of symptoms at baseline and after 4 and 8 weeks of treatment**

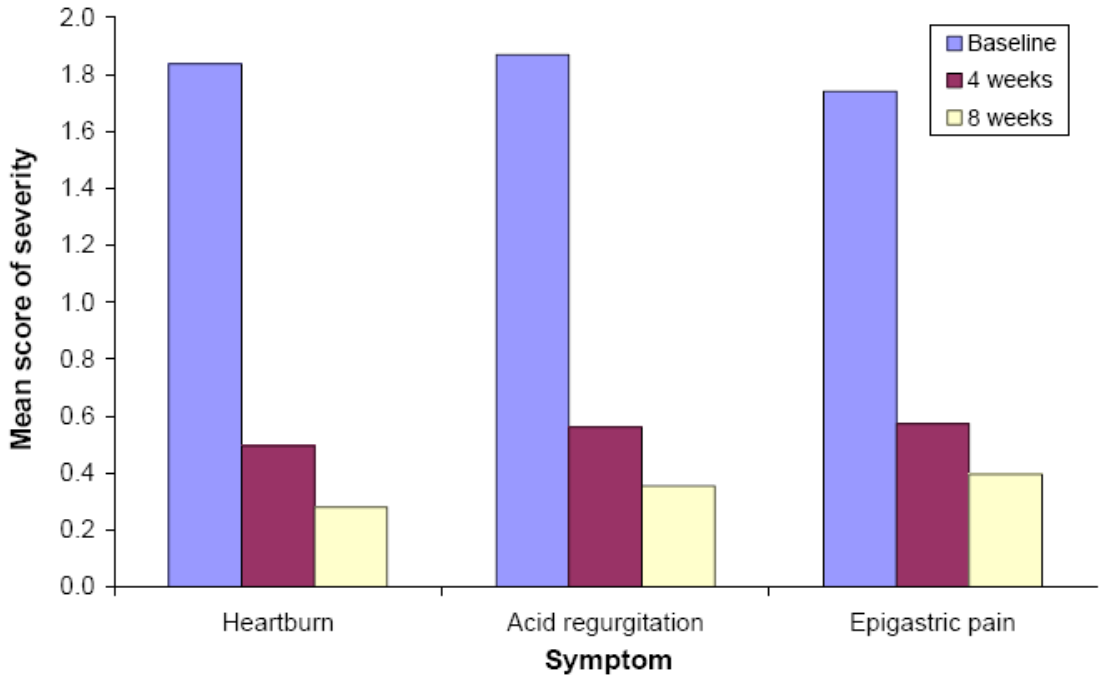

Table S6 Statistical analysis of changes from baseline to 4 and 8 weeks in GORD symptoms, full analysis set

	Baseline		Change from baseline		95% Cl of change	P value
	Mean	(SD)	Mean	(SD)		
4 weeks						
Frequency						
Heartburn	3.90	2.25	-3.08	2.32	(-3.34 , -2.82)	<.0001
Acid Regurgitation	3.92	2.39	-2.95	2.42	(-3.22 , -2.68)	<.0001
Epigastric Pain	3.74	2.48	-2.77	2.50	(-3.05, -2.49)	<.0001
Severity						
Heartburn	1.84	0.86	-1.34	1.03	(-1.46 , -1.23)	<.0001
Acid Regurgitation	1.87	0.95	-1.31	1.03	(-1.43 , -1.19)	<.0001
Epigastric Pain	1.74	0.97	-1.17	1.10	(-1.29 , -1.04)	<.0001
8 weeks						
Frequency						
Heartburn	3.90	2.25	-3.44	2.35	(-3.7 , -3.18)	<.0001
Acid Regurgitation	3.92	2.39	-3.28	2.51	(-3.56 , -3)	<.0001
Epigastric Pain	3.74	2.48	-3.16	2.52	(-3.44 , -2.88)	<.0001
Severity						
Heartburn	1.84	0.86	-1.56	1.01	(-1.67 , -1.44)	<.0001
Acid Regurgitation	1.87	0.95	-1.51	1.09	(-1.64 , -1.39)	<.0001
Epigastric Pain	1.74	0.97	-1.34	1.10	(-1.47 , -1.22)	<.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 3.90 days a week to 0.82 day a week at the end of the 8-week treatment period with esomeprazole (p<.0001). This corresponds to a mean reduction of 79 % 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<.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 0.82 day a week (mean change in frequency of heartburn from baseline –3.08 days, p<0.0001). This corresponds to a mean reduction of 79% in the frequency of heartburn.

Patient Reported Outcomes (PRO)

RDQ Global score

The global score was obtained by calculating the mean of all 12 item scores of the RDQ. There were significant improvements in the global scores from baseline to 4 weeks (mean change from baseline –2.03, p<0.0001, Table S7) and 8 weeks (mean change from baseline –2.34, p<0.0001, Table S8).

Table S7 Change in RDQ global score and dimension scores from baseline to 4 weeks, Full analysis set

	Baseline Visit 1	**Change after 4 weeks (Visit 2)**
Global Score		
N	305	305
Mean (SD)	2.78 (1.03)	-2.03 (1.12)
Median	2.67	-2
Range	0.33 , 5	-5 , 2.08
P - value		<0.0001
95% C.I: of Change		(-2.16 , -1.9)
Heartburn		
N	305	305
Mean (SD)	2.5 (1.27)	-1.93 (1.38)
Median	2.50	-2
Range	0 , 5	-5 , 2.5
P - value		< 0.0001
95% C.I: of Change		(-2.08 , -1.77)
Acid Regurgitation		
N	305	305
Mean (SD)	2.99 (1.21	-2.09 (1.32)
Median	3.00	-2.25

	Baseline Visit 1	Change after 4 weeks (Visit 2)
Range	0 , 5	-5 , 2.25
P - value		< 0.0001
95% C.I: of Change		(-2.24 , -1.94)
GORD dimension		
N	305	305
Mean (SD)	2.75 (1.08)	-2.01 (1.17)
Median	2.75	-2
Range	0 , 5	-5 , 2.25
P - value		< 0.0001
95% C.I: of Change		(-2.14 , -1.88)
Dyspepsia		
N	305	305
Mean (SD)	2.85 (1.38)	-2.07 (1.43)
Median	3.00	-2
Range	0 , 5	-5 , 1.75
P - value		< 0.0001
95% C.I: of Change		(-2.24 , -1.91)

Table S8 - Change in RDQ global score from baseline to 8 weeks, full analysis set

Global score	Baseline (Visit 1)	Change after 8 weeks (Visit 3)
Global score		
N	**305**	**305**
Mean (SD)	**2.78 (1.03)**	**-2.34 (1.12)**
Median	**2.67**	**-2.333**
Range	**0.33 , 5**	**-5 , 1.25**
P-value		**<0.0001**
95% C.I. Of change		**(-2.46 , -2.21)**

Global score calculated as a mean of 12 items 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.

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

GORD Impact Scale (GIS)

Forty eight percent of subjects treated with esomeprazole assessed their overall level of control as "well controlled" after 8 weeks of treatment using the GIS (Table S9)

Table S9 Number (%) of subjects with level of GORD control at baseline, 4 and 8 weeks derived from responses to GIS, full analysis set

Level of Control	Number (%) of patients (n = 317)					
	Baseline (visit 1)		4 weeks (visit 2)		8 weeks (visit 3)	
Very poorly controlled (0)	**22**	**(7.07 %)**	**0**	**(0%)**	**2**	**(0.64%)**
Poorly controlled (1-3)	**174**	**(55.95 %)**	**26**	**(8.36%)**	**10**	**(3.22%)**
Uncontrolled (4-5)	**85**	**(27.33%)**	**58**	**(18.65%)**	**28**	**(9%)**
Fairly well controlled (6-8)	**21**	**(6.75%)**	**101**	**(32.48%)**	**110**	**(35.37%)**
Well controlled (9)	**0**	**(0%)**	**112**	**(36.01%)**	**150**	**(48.23%)**
Missing	**9**	**(2.89%)**	**14**	**(4.5%)**	**11**	**(3.54%)**

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.

Summary of safety results

The mean exposure to esomeprazole 40 mg was 55,37 days. 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 subject population under study. None of the SAEs was assessed as casually related to the study drug. Any patient was discontinued due to DAE

Table S10 – Number (%) of patients who had a serious adverse event or an AE leading to discontinuation of study treatment, and total number of adverse events, safety analysis set

Category of adverse events	Number (%) of patients
Serious Adverse Events	
Serious Adverse Events leading to death	0
Serious Adverse Events not leading to death	4
Discontinuations of study treatment due to adverse event (DAE)	0
Causally related serious adverse event	0
Causally related DAE	0

Category of adverse events	Number (%) of patients
Serious Adverse Events	6
DAE	0
Causally related serious adverse event	0
Causally related DAE	0

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