AstraZeneca

Drug product:	Nexium 40/20	**SYNOPSIS**	
Drug substance(s):	Esomeprazole 40/20		
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Evaluating the benefit of continuous versus on demand Nexium® therapy: A randomised study on the efficacy of maintenance therapy in gastroesophageal reflux disease patients (BRILLIANT)

Study centre(s)

This study was conducted in 60 centres in The Netherlands.

Publications

A poster was presented at UEGW 2003 and NVGE (Dutch Society of Gastro-enterology) Fall Meeting 2003.

Study dates		**Phase of development**
First subject enrolled	10 October 2000	III
Last subject completed	28 February 2003	

Objectives

- **Primary objective**

  To compare the efficacy with regard to patient satisfaction, of on demand (i.e. "when needed") esomeprazole 40 mg once daily therapy and continuous esomeprazole 20 mg once daily therapy over a 6 month maintenance period, in gastro-esophageal reflux disease (GERD) patients. Before start of the maintenance therapy initial symptom relief has been achieved with esomeprazole 40 mg once daily enrolment therapy for 2,4 or 8 weeks.

Patient satisfaction will be evaluated separately for endoscopic negative patients, and for patients with reflux esophagitis grade A or B.

- **Secondary objectives**

  Evaluation of patient satisfaction for all randomised GERD patients, irrespective of evidence of inflammation. To compare the two maintenance treatment regimens with regard to Quality of Life and to study patients' dosing habits during on-demand treatment.

  Other secondary objectives include the healing phase: to determine the proportion of patients with sufficient symptom relief (i.e. heartburn relief), the proportion of patients satisfied with treatment, patients free of regurgitation and dysphagia after 2, 4 or 8 weeks treatment with esomeprazole 40 mg once daily.

  The safety and tolerability of esomeprazole were evaluated

Study design

This was a randomised, reference controlled, parallel group, investigator-blind multicentre study comparing the efficacy of esomeprazole 40 mg on demand with esomeprazole 20 mg once daily over a 6 month maintenance period, in gastro-esophageal reflux disease (GERD) patients.

Target subject population and sample size

Male and female subjects, aged between 18 and 80 years inclusive, with gastro-esophageal reflux disease (GERD), with reflux esophagitis (RO) grade A or B or endoscopic negative reflux disease (ENRD) patients, with moderate heartburn during the week, experiencing heartburn at least 3 of the last 7 days prior to visit 1.

A total of 225 randomised and evaluable subjects with endoscopic negative reflux disease and 225 randomised and evaluable subjects with reflux esophagitis grade A or B, derived from an estimated 300 recruited subjects, were required per treatment group for 80% power of detecting a 10% difference between groups with a 5% level of significance.

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

Esomeprazole (H199/18, Nexium®), 40 mg orally once daily, during healing phase and on demand during maintenance phase. Batch number: H 1365-01-03-01

Esomeprazole (H199/18, Nexium®), 20 mg orally once daily, during maintenance phase. Batch number: H 1370-01-02-01

Duration of treatment

Enrolment phase: 2, 4 or 8 weeks continuous esomeprazole 40 mg once daily treatment (depending on time to satisfaction and sufficient symptom relief)

Randomisation phase (maintenance phase): 6 months esomeprazole 40 mg once daily on demand or esomeprazole 20 mg once daily continuous treatment.

Criteria for evaluation (main variables)

Efficacy

Primary variable:

- Patient satisfaction at visit 4 for ENRD patients and RO patients

Secondary variables:

- Patient satisfaction at visit 4 for all GERD patients
- Heartburn symptoms at visit 2/2.1/2.2
- Satisfaction at visit 2/2.1/2.2
- Regurgitation and dysphagia symptom score at visits 2/2.1/2.2
- Symptom score in the enrolment phase diary card.
- Quality of Life, measured with QOLRAD quality of life questionnaire at visit 1, randomisation and visit 4.
- Dosing habits (no. of tablets used, symptom score in the maintenance phase diary card).
- GERD related (in)direct costs in the maintenance phase

Safety

Standard safety assessments included adverse event reports and physical examination.

Statistical methods

The proportions of satisfied patients (ENRD patients, RO patients and all GERD patients) were analysed with a $\chi 2$ test at a significance level of 5%. Also 95% confidence intervals of the treatment differences and of the separate proportions were determined (using the t distribution).

Proportion of patients with sufficient symptom relief, proportion of satisfied patients, proportion of patients free of regurgitation and free of dysphagia after 2, 4 and 8 weeks of treatment with esomeprazole 40 mg were analysed descriptively by calculating 95% confidence limits using the t-distribution.

Time to sustained symptom relief during the enrolment phase was analysed by determining the median time to sustained symptom relief using the life table approach (Kaplan Meier). Confidence limits of 95% were determined using Greenwood's formula with adjustment by Kalbfleisch and Prentice for estimating variance.

The Quality of Life dimensions were analysed using one-way fixed effect analysis of variance with factor treatment in the model and baseline values as covariate. The difference between two treatments were calculated by using least square estimates resulting from the analysis of variance model. Confidence limits of 95% of the difference between least square means were calculated using the t-distribution.

Dosing habits for on demand patients, adverse events, costs and the exploratory variables were analysed descriptively.

Patient population

In this study 598 endoscopic negative patients and 574 patients with erosive reflux esophagitis (in total 1172) were included. Of these 1052 patients were randomised (527 endoscopic negative patients and 525 patients with erosive reflux esophagitis). The subject population is described in table S1 below.

Table S1 Patient population and disposition

		Not randomised	Continuous	On demand	Total
Population					
N randomised		120	528	524	1172
Demographic characteristics					
Sex (n and	Male	54 (45%)	278 (53%)	293 (56%)	625 (53%)
% of subjects)	Female	66 (55%)	250 (47%)	231 (44%)	547 (47%)
Age (years)	Mean (SD)	47.2 (14.6)	48.6 (13.6)	48.9 (13.2)	48.6 (13.5)
	Range	19 to 77	17 to 82	19 to 80	17 to 82
Race (n and	Caucasian	113 (94%)	516 (98%)	513 (98%)	1142 (97%)
% of subjects)	Black	4 (3%)	5 (1%)	5 (1%)	14 (1%)
	Oriental	3 (3%)	5 (1%)	5 (1%)	13 (1%)
	Other	0 (0%)	2 (0%)	1 (0%)	3 (0%)
Baseline characteristics					
Quetelet Index	Mean (SD)	25.9 (4.91)	26.7 (3.81)	27.1 (3.97)	26.8 (4.02)
Hp-status known	No	66 (55%)	246 (47%)	233 (44%)	545 (47%)
	Yes	54 (45%)	282 (53%)	291 (56%)	627 (53%)
If yes, result Hp	Negative	42 (78%)	204 (72%)	213 (73%)	459 (73%)
	Positive	12 (22%)	78 (28%)	78 (27%)	168 (27%)

		Not randomised	Continuous	On demand	Total
Disposition					
N (%) of subjects who	Completed	0 (0%)	477 (90%)	472(90%)	949 (81%)
	Discontinued	120 (100%)	51 (10%)	52 (10%)	223 (19%)
N analysed for safety[a]		116	528	524	1168
N analysed for efficacy (ITT)			528	524	1052
N analysed for efficacy (PP)			415	388	803

[a] Number of subjects 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

Efficacy results

On the primary efficacy variable patient satisfaction, no statistical differences were found between the on demand treatment regimen and the once daily treatment regimen. 88.97% of the patients regardless of their endoscopic status were satisfied with the maintenance treatment.

Table S2 Patient satisfaction with maintenance treatment

Percentage of satisfied patients	Reflux Esophagitis		ENRD	
	PP	ITT	PP	ITT
Continuous	95.45%	88.37%	96.31%	90.74%
On demand	97.37%	87.27%	95.45%	89.49%
Total	96.39%	87.81%	95.90%	90.13%

Percentage of satisfied patients (ITT)	All GERD patients
Continuous	89.58%
On demand	88.36%
Total	88.97%

Table S3 GERD symptoms and satisfaction during enrolment

Summary				
		After 2 weeks	**After 4 weeks**	**After 8 weeks**
Sufficient symptom relief	Reflux esophagitis	70.91%	85.54%	90.59%
	ENRD	71.31%	82.89%	88.09%
Satisfied	Reflux esophagitis	90.42%	92.86%	94.20%
	ENRD	89.77%	90.44%	92.11%
Free of regurgitation	Reflux esophagitis	78.92%	84.32%	85.37%
	ENRD	82.55%	86.07%	88.26%
Free of dysphagia	Reflux esophagitis	91.64%	94.60%	95.12%
	ENRD	92.45%	93.96%	94.46%

No differences were observed for reported GERD symptoms during the enrolment phase between reflux esophagitis and ENRD patients.

Table S4 Difference in Quality of life after 6 months of maintenance treatment

Quality of life, **Difference between continuous treatment minus on demand**	**Reflux Esophagitis**		**ENRD**	
	Mean	**P-value**	**Mean**	**P-value**
Emotional distress	0.21	(0.0055)	0.22	(0.0004)
Sleep disturbance	0.28	(0.0004)	0.26	(0.0001)
Food/Drink problems	0.51	(<0.0001)	0.42	(<0.0001)
Physical/social functioning	0.24	(0.0001)	0.21	(<0.0001)
Vitality	0.50	(<0.0001)	0.38	(<0.0001)

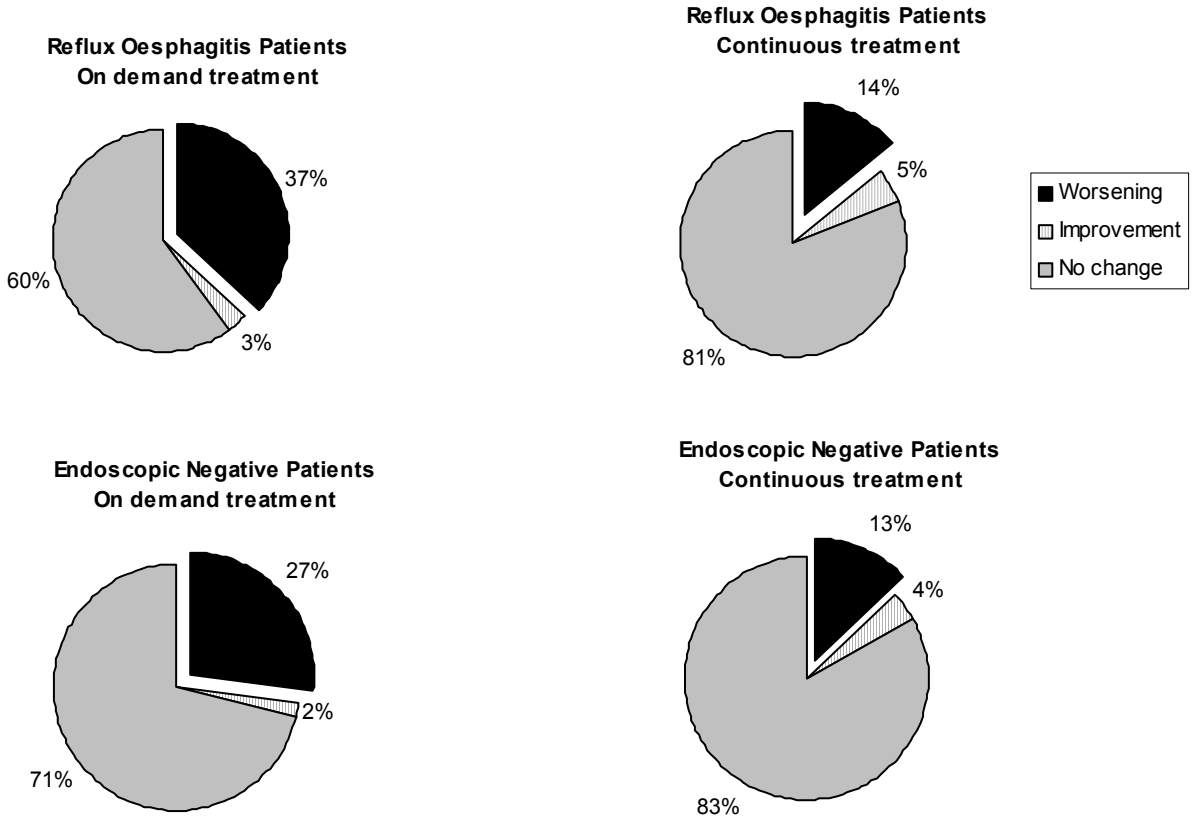
In all dimensions of the Quality of Life, a difference in favour of the continuous treatment regimen was found in both Reflux Esophagitis patients and Endoscopic Negative patients. The difference was more profound in the Reflux Esophagitis group.

Median time to sustained symptom relief for patients without esophagitis was 4 days. For patients with esophagitis, the median time to sustained symptom relief was 3 days, indicating that patients with reflux esophagitis responded quicker to the esomeprazole healing phase treatment.

Based on the patient's diary, endoscopic negative patients randomised to the on demand treatment group, took on average 1 tablet every 7 days. A higher intake of 1 tablet every 6 days was found in the patients with reflux esophagitis. The median intake was higher and was for both groups one tablet every 2-3 days.

The difference in heartburn scores after 6 months of maintenance treatment was calculated. Especially in the on demand treated patients, the Reflux Esophagitis patients showed a larger deterioration over the six months maintenance period than the Endoscopic Negative GERD patients. In both groups of patients, the once daily treatment regimen seemed more able to maintain the improvement in GERD symptoms after an initial healing phase.

Figure S1 **Difference in heartburn scores after 6 months of maintenance treatment**



Safety results

Table S5 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]
	Nexium Total
Any adverse events	366 (31%)
Serious adverse events	
Serious adverse events leading to death	2 (0%)
Serious adverse events not leading to death	24 (2%)
Discontinuations of study treatment due to adverse events	41 (4%)
	Total number of adverse events
Adverse events	644
Serious adverse events	27

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Table S6 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event
	Nexium Total (n=1168)
Headache	50 (4%)
Diarrhoea	34 (3%)
Nausea	33 (3%)
Abdominal pain	30 (3%)
Infection viral	26 (2%)
Flatulence	24 (2%)

[a] Events with a total frequency of ≥2% across all treatment groups are included in this table.

Date of the report 22 Feb 2005