AstraZeneca

Drug product	Nexium	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
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Clinical Study Report

Study centre(s)

A multi-center study with 61 centres in Austria (6), France (27), Germany (14), South Africa (9) and Spain (5).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	24 August 2001	Therapeutic confirmatory (III)
Last subject completed	07 November 2002	

Objectives

The primary objective was to compare on demand* with continuous treatment of endoscopy negative subjects with gastroesophageal reflux disease (GERD), with esomeprazole 20 mg once daily, with regards to willingness to continue in the study as a result of satisfactory treatment over a six-month long term management period, after initial symptom relief.

(* On demand = taken as needed by the subjects to adequately control their reflux disease)

Secondary objectives were:

- To study the reasons for subjects discontinuing from treatment
- To assess drug usage
- To assess aspects of Health-Related Quality of Life (HRQL)
- To assess aspects of treatment satisfaction
- To assess safety and tolerability

Study design

This was an open, randomised, parallel group, and multicentre study. Subjects presenting at General Practitioner (GP) clinics and gastrointestinal (GI) specialists / hospitals with direct referrals with symptoms suggestive of GERD (with heartburn as the predominant symptom) and without esophagitis (ruled out by endoscopy) were eligible to enter into the study. All subjects had an initial treatment period of 4 weeks with esomeprazole 20 mg once daily. Subjects with persisting symptoms after 4 weeks of treatment left the study and were treated according to clinical routines.

Subjects who were free from heartburn (7 symptom free days in the last week of the initial treatment phase) at 4 weeks, were randomised into any of the two treatment groups: on demand treatment with 20 mg esomeprazole once daily when needed, or continuous treatment with 20 mg esomeprazole once daily, for six months. All subjects were assessed for their *H. pylori* status at the beginning of the study.

Target subject population and sample size

Patients presenting at GP clinics and GI specialists / hospitals with direct referrals with symptoms suggestive of GERD (heartburn as their predominant symptom) and without esophagitis (ruled out by endoscopy) were eligible to enter into the study.

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

Esomeprazole, 20 mg once daily or when needed, per oral administration.

Duration of treatment

All eligible subjects had 4 weeks of initial treatment with esomeprazole 20 mg once daily followed by a 6 month treatment period after randomisation to either esomeprazole 20 mg once daily on demand or continuous.

Criteria for evaluation (main variables)

Efficacy

The primary objective was to compare on demand with continuous treatment of endoscopy negative subjects with GERD with esomeprazole 20 mg, with regards to willingness to continue in the study as a result of satisfactory treatment over a six-month long term management period, after initial symptom relief.

Secondary objectives were:

- To study the reasons for subjects discontinuing from treatment
- To assess drug usage
- To assess aspects of Health-Related Quality of Life (HRQL)
- To assess aspects of treatment satisfaction

Safety

Safety assessments included adverse event (AE) reports and clinical laboratory data (Haematology and Clinical Chemistry). Measurement of vital signs and a physical examination were done at baseline. AEs were recorded during the treatment period and serious adverse events (SAEs) were recorded during the whole study.

Statistical methods

The primary endpoint was evaluated by the calculation of a one-sided 95% confidence interval (CI) for the difference between treatments in proportion of subjects who discontinued due to unsatisfactory treatment.

Treatment satisfaction questions had two-sided 95% CI for the difference between treatments in proportions of satisfied subjects and of the separate proportions calculated.

Subject's drug use (dosing habits) was described using descriptive statistics, frequency tables.

For Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia Questionnaire (QOLRAD) two-sided 95% CI for the change from baseline were calculated.

Presence and severity of upper GI symptoms (heartburn, acid regurgitation, dysphagia and epigastric pain) as well as frequency of heartburn were presented using frequency tables.

The primary endpoint was analysed both for an intention to treat (ITT) population and for a Per Protocol (PP) population. The conclusion was based on the ITT analysis.

All safety variables were presented descriptively.

Subject population

Table S 1 Subject population and disposition

		On demand		Continuous		Total	
Population							
n randomised (n planned)		301	(275)	297	(275)	598	(550)
Demographic characteristics							
Sex (n and % of subjects)	Male	122	(40.5%)	130	(43.8%)	252	(42.1%)
	Female	179	(59.5%)	167	(56.2%)	346	(57.9%)
Age (years)	Mean (SD)	48.2	(13.6)	47.6	(15.1)	47.9	(14.4)
	Range	20 to 82		20 to 80		20 to 82	
Race (n and % of subjects)	Caucasian	259	(86.0%)	255	(85.9%)	522	(87.3%)
	Black	14	(4.7%)	10	(3.4%)	24	(4.0%)
	Oriental	1	(0.3%)	4	(1.3%)	5	(0.8%)
	Other	27	(9.0%)	28	(9.4%)	55	(9.2%)
Baseline characteristics							
Days with heartburn	4 days	26	(8.6%)	31	(10.4%)	57	(9.5%)
	5 days	55	(18.3%)	46	(15.5%)	101	(16.9%)
	6 days	46	(15.3%)	42	(14.1%)	88	(14.7%)
	7 days	174	(57.8%)	178	(59.9%)	352	(58.9%)
Severity of heartburn	Mild	21	(7.0%)	19	(6.4%)	40	(6.7%)
	Moderate	165	(54.8%)	153	(51.5%)	318	(53.2%)
	Severe	115	(38.2%)	125	(42.1%)	240	(40.1%)
Hp status	Negative	176	(58.5%)	166	(55.9%)	342	(57.2%)
	Positive	125	(41.5%)	130	(43.8%)	255	(42.6%)
	Missing	0	(0.0%)	1	(0.3%)	1	(0.2%)
Disposition							
n (%) of subjects who	completed[a]	282	(93.7%)	268	(90.2%)	550	(92.0%)
	discontinued[a]	19	(6.3%)	29	(9.8%)	48	(8.0%)
n analyzed for APT/safety[b]						674[c]	
n analyzed for efficacy (ITT)		301		297[d]		598	
n analyzed for efficacy (PP)		251		232		483	

[a] Number of randomised subjects who completed and discontinued
[b] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
[c] 687 subjects are included in the evaluation of AE data
[d] 3 randomised subjects never took any study drug and are therefore not presented in the AE evaluation

ITT Intention to treat; n Number; PP Per-protocol, Hp Helicobacter pylori
Other comprised of mixed race (98%) and Half-caste (2%)

Efficacy results

The proportions of subjects who discontinued due to unsatisfactory treatment are presented in Table S2. The one-sided 95% CI for the difference between treatments regarding the primary endpoint, shown by the upper bound of the two-sided 90% CI, is given in Table S3.

Table S 2 Proportion of subjects who discontinued due to unsatisfactory treatment, estimates and 90% and 95% exact confidence intervals, ITT

Treatment	Estimate	90% CI		95% CI	
		Lower	Upper	Lower	Upper
on demand	6.3%(19/301)	4.2%	9.1%	3.8%	9.7%
continuous	9.8%(29/297)	7.1%	13.1%	6.6%	13.7%

Treatment with esomeprazole 20 mg

Table S 3 Difference between on demand and continuous treatment in proportion of subjects who discontinued due to unsatisfactory treatment, estimate and 90% confidence intervals (normal approximation), ITT

Treatment	Estimate	90% CI	
		Lower	Upper[a]
on demand - continuous	-3.5%	-7.1%	0.2%

Treatment with esomeprazole 20 mg

[a] Statistical non-inferiority is established if the upper confidence bound of the difference (on demand - continuous) is < 10%

The upper confidence bound of the difference between on demand and continuous treatment is less than 10%-points, thus it can be concluded that on demand treatment is not inferior to continuous treatment regarding the proportion of subjects who discontinue due to unsatisfactory treatment.

Safety results

The frequency of AE was similar in the 2 randomised treatment groups.

SAEs were reported by 4 subjects in the initial treatment phase and by 15 subjects on randomised treatment (4 subjects in the on demand group and 11 subjects in the continuous group).

All SAEs were assessed as not related to study drug by the investigator.

The most commonly reported AEs were from the organ class gastrointestinal (GI) system disorders.

Discontinuation of study treatment due to AE was reported by 18 subjects in the initial treatment phase, 1 subject in the on demand group and 7 subjects in the continuous group.

There were no AEs classified as other significant AEs.

Isolated changes both within and outside the laboratory reference ranges were seen for most of the safety laboratory variables. There were no clinically significant trends found in any of the treatment groups.

All study treatment regimens were well tolerated and there were no findings that raised any safety concerns. There were a few more SAEs reported in the continuous treatment group compared to the on demand treatment group.

Table S 4 Number (%) of subjects who had at least 1 AE in any category, and total numbers of AEs (safety population)

Category of AEs	N(%) of subjects who had an AE in each category					
	Initial treatment phase		Randomised subjects			
			on demand		continuous	
	(n=687)		(n=301)		(n=294)	
Any AEs[a]	115	(16.7)	109	(36.2)	104	(35.4)
SAEs	4	(0.6)	4	(1.3)	11	(3.7)
SAEs leading to death	0		0		0	
SAEs not leading to death	4	(0.6)	4	(1.3)	11	(3.7)
Discontinuations of study treatment due to AEs	18	(2.6)	1	(0.3)	7	(2.4)
Other significant AE	0		0		0	
Severe AEs	9	(1.3)	11	(3.7)	14	(4.8)
	Total number of AEs					
Any AEs[b]	156		179		197	
SAEs[b]	4		5		13	
Discontinuations AEs[b]	29		1		8	
Other significant AE[b]	0		0		0	
Severe AEs	13		13		15	

[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.

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

Table S 5 **Number (%) of subjects with the most commonly reported AEs (preferred term), sorted by decreasing order of frequency in all randomised subjects (safety population)**

Preferred term	Initial treatment phase		Randomised subjects on demand		continuous	
	(n=687)		(n=301)		(n=294)	
	n	(%)	n	(%)	n	(%)
Flatulence	12	(1.7)	15	(5.0)	12	(4.1)
Infection viral	5	(0.7)	12	(4.0)	8	(2.7)
Abdominal pain	9	(1.3)	10	(3.3)	9	(3.1)
Gastroenteritis	2	(0.3)	7	(2.3)	9	(3.1)
Diarrhoea	13	(1.9)	6	(2.0)	9	(3.1)
Constipation/constipation aggravated	11	(1.6)	9	(3.0)	5	(1.7)
Respiratory infection	8	(1.2)	7	(2.3)	6	(2.0)
Back pain	3	(0.4)	5	(1.7)	7	(2.4)
Headache	10	(1.5)	5	(1.7)	7	(2.4)
Arthralgia	1	(0.1)	2	(0.7)	6	(2.0)
Nausea	9	(1.3)	6	(2.0)	2	(0.7)

AEs experienced by at least 2% of the subjects in any treatment group are included in this table

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