AstraZeneca

Drug product	Nexium®	**SYNOPSIS**	
Drug Substance	Esomeprazole		
Edition Number	1		
Study Code	SD-NEE-0003		
Date	24 November 2004		

A randomized, double-blind, parallel-group multicentre efficacy and safety phase IIB pilot study of esomeprazole 40 mg twice daily versus placebo twice daily in adult asthmatics treated for 4 months

Study centre(s)

This study was conducted in 12 countries (122 centres): Argentina (10 centres), Brazil (6 centres), Bulgaria (7 centres), Canada (7 centres), Czech Republic (8 centres), Finland (4 centres), Hungary (6 centres), Italy (9 centres), Mexico (5 centres), Romania (8 centres), Sweden (2 centres), and the US (50 centres).

Publications

None at time of writing this report.

Study dates

First patient enrolled: 28 October 2002

Last patient completed: 30 April 2004

Phase of development

Therapeutic exploratory (IIB)

Objectives

Primary objective

The primary objective was to determine whether Nexium® [1] (esomeprazole) 40 mg twice daily (b.i.d.) had an anti-asthmatic effect compared to placebo in patients with persistent asthma, regularly treated with anti-inflammatory medication, by evaluation of:

- change in morning peak expiratory flow (mPEF; **primary variable**) from baseline (mean of the last 7 days of the run-in period) to end of treatment period (mean of the last 28 days of the treatment period)
- change in evening PEF (ePEF) from baseline to end of treatment period
- change in daytime asthma symptom score from baseline to end of treatment period
- change in night-time asthma symptom score from baseline to end of treatment period
- change in percentage of nights with night-time awakening due to asthma from baseline to end of treatment period
- change in percentage of days with PEF variability (fall in PEF over night) ≥15% from baseline to end of treatment period
- change in frequency of use of inhaled short-acting β_2-agonists (SABAs) from baseline to end of treatment period
- change in forced expiratory volume in 1 second (FEV_1) from randomization (Visit 2) to last visit (Visit 6)
- time to asthma exacerbation
- change in Asthma Control Questionnaire (ACQ, 5 questions) score from randomization (Visit 2) to last visit (Visit 6)

[1] Nexium is a registered trademark of the AstraZeneca group of companies.

- change in Asthma Quality of Life Questionnaire, standardized version (AQLQ(S)) score, for each domain and overall, from from randomization (Visit 2) to last visit (Visit 6).

Secondary objective

The secondary objective was to assess the safety and tolerability of Nexium 40 mg b.i.d. versus placebo during 16 weeks in patients with persistent asthma, regularly treated with anti-inflammatory medication, by evaluation of:

- incidence, severity, and type of Adverse Events (AEs)

- incidence of clinically important changes in haematology, clinical chemistry, physical examination and pulse and blood pressure (vital signs).

Study design

This was a multinational and multicentre pilot study with a randomized, double-blind, placebo-controlled, parallel-group design, starting with a 2-week run-in period and followed by a 16-week treatment period assessing the efficacy and safety of Nexium 40 mg given b.i.d. versus placebo. Patients with persistent asthma associated with either a history of night-time awakenings, increased overnight fall in PEF, or documented gastro-oesophageal reflux (GOR) symptoms were included in the study.

Target patient population and sample size

Non-smoking, asthmatic patients of either sex, aged 18 to 70 years, with pre-bronchodilator FEV_1 ≥55% and ≤80% of predicted normal (P.N.), and on a constant dose of asthma maintenance medication for at least 30 days prior to enrolment. The patients were stratified into 3 groups based on their nocturnal respiratory symptoms and GOR symptoms to establish the potential for respiratory-associated night-time awakening as a clinical surrogate marker for GOR-associated asthma:

- Stratum 1: Patients **with** nocturnal respiratory symptoms (either of the two categories defined below) but **without** GOR signs/symptoms.

    - Night-time awakening with associated respiratory symptoms ≥1 episode(s) during the last 7 days of the run-in period.

    - A fall in PEF from bedtime to morning awakening of ≥15%, as measured and recorded by the patient, at least twice during the last 7 days of the run-in period.

- Stratum 2: Patients **without** nocturnal respiratory symptoms (as defined for group 1) but **with** GOR signs and/or symptoms, consisting of any of the categories defined below.

  - Any patient who could temporally correlate heartburn symptom preceding asthma symptoms within 1 hour. This observed association had to have occurred twice within 3 months prior to enrolment.

  - On average, ≥1 episode(s) per week of acid regurgitation, of any severity, within 3 months prior to enrolment.

  - On average, ≥2 episodes per week of heartburn within 3 months prior to enrolment.

  - A documented history of erosive oesophagitis or Barrett's oesophagus (with no history of dysplasia or biopsies indefinite for dysplasia) within 1 year prior to enrolment.

  - A documented history of an abnormal 24-hour pH monitoring. This should consist of a 24-hour pH monitoring, measured 5 cm proximal to the lower oesophageal sphincter, with an average pH <4, >4% of the total time, and/or a good correlation between patient's recorded complaint of heartburn and observed acid-reflux episode(s) on pH monitoring.

- Stratum 3: Patients **with** nocturnal respiratory symptoms **and** GOR signs and/or symptoms (see Strata 1 and 2 for requirements).

A total of 300 evaluable patients in each of the two treatment arms (Nexium and placebo) was required for 80% power of detecting a difference regarding change in mPEF, assuming a true mean difference of 11.5 L/min and a standard deviation of 50 L/min.

A total of 100 patients per arm within each stratum was required for 80% power of detecting a difference regarding change in mPEF, assuming a true mean difference of 20 L/min and the same standard deviation as above.

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

Nexium 40 mg capsules (batch H 1222-04-01-10) administered orally b.i.d., or placebo capsules for Nexium (batch H 0459-06-03-09) administered orally b.i.d. Antacid tablets with an acid-binding capacity of ≤16 mmol HCl was used as heartburn rescue medication, and purchased locally in the participating countries.

Duration of treatment

There was a 2-week run-in period, followed by a 16-week treatment period.

Criteria for evaluation (main variables)

The full analysis set, ie, all randomized patients, was used in the efficacy analyses. The safety analyses were based on all patients who took at least one dose of the invewstigational products (ie, Nexium or placebo).

Efficacy and pharmacokinetics

Efficacy was measured as follows.

- Primary variable: change in mPEF from baseline (mean of the last 7 days of the run-in period) to the end of treatment period (mean of last 28 days of treatment period).
- Secondary variables:
  - change in ePEF from baseline to end of treatment
  - change in daytime asthma symptom score from baseline to end of treatment
  - change in night-time asthma symptom score from baseline to end of treatment
  - change in percentage of nights with night-time awakening due to asthma from baseline to end of treatment
  - change in percentage of nights with PEF variability ≥15% from baseline to end of treatment
  - change in frequency of use of inhaled SABAs from baseline to end of treatment
  - change in FEV_1 from randomization to last visit
  - time to asthma exacerbation
  - change in ACQ (5 questions) score from randomization to last visit.

The pharmacokinetics of esomeprazole was not investigated in this study.

Health-related quality of life

Change in overall score and in each domain score from randomization to last visit was measured by the AQLQ(S).

Safety

The safety assessment included evaluation of:

- the incidence, severity, and type of AEs.
- haematology, clinical chemistry, and vital signs.

Statistical methods

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

The baseline period mean was defined as the mean during the last 7 days of the run-in period. The end of treatment period mean was defined as the mean during the last 28 days of the treatment period. Both of these period means were calculated regardless of the actual duration of each period. The change from baseline to end of treatment was calculated as the difference between these two period means. In order to assess the sensitivity of the chosen period duration for treatment period, a secondary analysis was also performed where the treatment period mean was calculated using all available data during treatment period.

The change from run-in to treatment in period means was analysed using an analysis of variance (ANOVA) model with treatment, stratum, treatment by stratum interaction, and country as factors, and with the run-in period mean as a covariate. When estimating the overall treatment difference from this model, strata were given equal weight (regardless of actual size). This is referred to as the main analysis model. To check the influence of this weighting on the overall treatment difference, the same model was also used in an alternative analysis but with exclusion of the treatment by stratum interaction factor. This is referred to as the alternative analysis model.

Patients who had been using LABA, either as a monoproduct or as a combination product, at any time 4 weeks prior to randomization was analysed as a subgroup.

The AEs were analysed at AstraZeneca by means of descriptive statistics and qualitative analysis. Results from laboratory safety measurements and vital signs measurements were analysed primarily by means of descriptive statistic within the framework of the standard laboratory safety evaluation at AstraZeneca.

Patient population

Demography and baseline characteristics for the randomized population are presented in Table S1.

Table S1 Patient population and disposition

		Nexium 40 mg b.i.d.	Placebo	Total
Population				
N randomized (n planned)		387 (300)	383 (300)	770 (600)
-N Stratum 1		101 (100)	100 (100)	201 (200)
-N Stratum 2		112 (100)	107 (100)	219 (200)
-N Stratum 3		174 (100)	176 (100)	350 (200)
Demographic characteristics in the whole population				
Sex (n and % of patients)	Male	109 (28%)	127 (33%)	236 (31%)
	Female	278 (72%)	256 (67%)	534 (69%)
Age (years)	Mean	44.7	44.8	44.8
	Range	19-71	18-70	18-71
Race (n and % of patients)	Caucasian	309 (80%)	308 (80%)	617 (80%)
	Black	18 (5%)	13 (3%)	31 (4%)
	Oriental	1 (<0.5%)	0	1 (<0.5%)
	Other	59 (15%)	62 (16%)	121 (16%)
N (%) of patients on inhaled GCS at entry		380 (98%)	376 (98%)	756 (98%)
-Daily dose of GCS (μg)	Mean	632	607	620
	Range	42-1600	44-2000	42-2000
N (%) of patients on LABA		145 (37%)	162 (42%)	307 (40%)

(Continued)

Table S1 Patient population and disposition

		Nexium 40 mg b.i.d.	Placebo	Total
Baseline characteristics in the whole population				
Mean FEV_1 (L)		2.052	2.082	2.067
FEV_1 (% P.N.)		66.2	66.5	66.3
FEV_1 reversibility (%)		24.6	23.3	23.9
Mean no. of heartburn episodes/week				
-Stratum 1		0.6	0.5	0.6
-Stratum 2		2.8	3.7	3.3
-Stratum 3		2.9	3.0	2.9
Disposition in the whole population				
N (%) of patients who:	Completed	322 (83%)	302 (79%)	624 (81%)
	Discontin.	64 (17%)	79 (21%)	143 (19%)
	Not treated or no data on treatment	1 (0.3%)	2 (0.5%)	3 (0.4%)
N analysed for safety[a]		386	381	767
N analysed for efficacy		387	383	770
N analysed in the primary variable analysis[b]		386	374	760

a Number of patients who took at least one dose of investigational product and had at least one data point after dosing.

b Less number of patients as data were missing in this analysis compared to the number analysed based on the ITT principle.

Efficacy and pharmacokinetic results

The pharmacokinetics of esomeprazole was not investigated in this study.

Results for the primary variable, mPEF, and the secondary variable ePEF, is summarized in Table S2.

Table S2 Morning and evening PEF

	mPEF (L/min) Mean treatment diff. (Nexium vs. placebo)	P-value	ePEF (L/min) Mean treatment diff. (Nexium vs. placebo)	P-value
1) Main analysis model. Based on mean from last 28 days of treatment.	6.3	0.061	5.9	0.078
2) Main analysis model. Based on mean from whole treatment period.	5.6	0.042	5.4	0.053
3) Alternative analysis model. Based on mean from last 28 days of treatment.	6.5	0.047	6.9	0.033
4) Patients on LABA at randomization. Main analysis model. Based on mean from last 28 days of treatment.	12.2	0.017	11.1	0.024

Table S3 Morning and evening PEF, by Stratum

	Stratum	mPEF (L/min) Mean treatment diff. (Nexium vs. placebo)	P-value	ePEF (L/min) Mean treatment diff. (Nexium vs. placebo)	P-value
1) Main analysis model. Based on mean from last 28 days of treatment.	1	3.6	0.57	-0.3	0.96
	2	8.3	0.17	6.7	0.27
	3	7.0	0.15	11.2	0.020
2) Main analysis model. Based on mean from whole treatment period.	1	2.6	0.62	1.3	0.81
	2	5.6	0.27	4.7	0.35
	3	8.7	0.030	10.2	0.012
4) Patients on LABA at randomization. Main analysis model. Based on mean from last 28 days of treatment.	1	8.1	0.41	5.4	0.57
	2	13.6	0.11	8.8	0.28
	3	14.8	0.065	19.0	0.015

Table S2 shows that the estimated treatment difference in mPEF for patients treated with 40 mg Nexium b.i.d and placebo was approximately 6 L/min, considering the whole study population. As seen in the table, the different analyses made for the whole study population gave similar results, both in terms of estimated differences between Nexium and placebo as well as for the p-value for the difference. In fact, the size of the p-value for the difference between Nexium and placebo was more dependent on individual patients than the choice of analysis model. When investigating a subgroup of patients on LABA at inclusion in the study, the improvement in mPEF was larger, 12 L/min, and statistically significant. Regardless of analysis used, the observed effect was more pronounced in Strata 2 and 3, ie, patients having GOR symptoms, as shown in table S3

For the secondary variable ePEF, the result was of the same magnitude as for mPEF (Table S2 and S3) while the remaining secondary variables did not provide evidence of an effect of Nexium in comparison with placebo.

Safety results

Table S4 Number (%) of patients who had at least one Adverse Event (AE) in any category, and total numbers of AEs (safety analysis set)[a]

Category of Adverse Event	Number (%) of patients who had at least one Adverse Event (AE) in each category[a]		
	Nexium 40 mg b.i.d. (n=386)	**Placebo (n=381)**	**Total (n=767)**
Any AEs	166 (43%)	171 (45%)	337 (44%)
Serious Adverse Events (SAEs)	4 (1%)	4 (1%)	8 (1%)
-SAEs leading to death	0	0	0
-SAEs not leading to death	4 (1%)	4 (1%)	8 (1%)
Discontinuations of study treatment due to Adverse Events (DAEs)	24 (6%)	31 (8%)	55 (7%)
Other significant Adverse Events (OAEs)	0	0	0
	Total number of AEs		
	Nexium 40 mg b.i.d.	**Placebo**	**Total**
AEs	306	288	594
SAEs	5	4	9
OAEs	0	0	0

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Table S5 **Number (%) of patients with the most commonly reported[a] Adverse Events, sorted in descending order of frequency as summarized over all treatment groups (safety analysis set)**

Adverse Event (preferred term)	Nexium 40 mg b.i.d. (n=386)	Placebo (n=381)	Total (n=767)
Asthma	23 (6%)	24 (6%)	47 (6%)
Nasopharyngitis	23 (6%)	22 (6%)	45 (6%)
Headache	25 (6%)	17 (4%)	42 (5%)

a Events with a total frequency of ≥4% across all treatment groups are included in this table.

The number of patients with reported non-serious AEs were similar for both groups. The most commonly reported AEs were asthma, nasopharhyngitis, and headache. There were few serious AEs in both groups. No deaths occurred. The number of patients who discontinued due to an AE were similar for both groups.

Date of the report

24 November 2004