Drug Product	Nexium®	**SYNOPSIS**	
Drug Substance	Esomeprazole		
Edition Number	1.0		
Study Code	SD-NED-0021		
Date	15 December 2005		

Supportive Test for Acid-Related Symptoms (STARS I) with esomeprazole and a following 7-week, double-blind, randomized, placebo-controlled treatment period in subjects with upper gastrointestinal symptoms and with normal findings at esophagogastroduodenoscopy

Study centre(s)

This study was conducted at 190 health-care centres or similar facilities in 17 countries: Argentina (7 centres), Belgium (11 centres), Brazil (8 centres), Canada (33 centres), Denmark (8 centres), France (16 centres), Germany (11 centres), Greece (5 centres), Iceland (5 centres), Italy (10 centres), Norway (30 centres), Romania (4 centres), Singapore (4 centres), South Africa (9 centres), Spain (5 centres), Sweden (23 centres), and Switzerland (1 centre).

Publications

Abstract submitted to the World Congress of Gastroenterology, Montreal, Canada, 2005, and to the United European Gastrointestinal Week, Copenhagen, Denmark, 2005. See Appendix 12.1.11.

Study dates

First patient enrolled: 7 December 2002

Last patient completed: 13 January 2005

Phase of development

Therapeutic confirmatory (IIIA).

Objectives

The primary objective of the study was to evaluate symptom response (ie, symptoms of pain or burning centred in the upper abdomen) to a 1-week test as a tool for predicting responders at the end of an 8-week treatment period in patients with normal findings at esophagogastroduodenoscopy (EGD). The 8-week treatment period included the 1-week test of esomeprazole 40 mg once daily (od) or 40 mg twice daily (bid) followed by 7 weeks of treatment with esomeprazole 40 mg od or placebo.

The symptom response at the end of the 1-week test was defined as the sum of the symptom scores during the last 3 days.

A responder after 8 weeks of treatment was a patient whose sum of symptom scores during the last 7 days was 0 or 1.

The secondary objectives of the study were:

1. To evaluate symptom response (ie, symptoms of pain or burning centred in the upper abdomen) to a 1-week test as a tool for predicting responders at the end of a 4-week treatment period. The treatment period included the 1-week test of esomeprazole 40 mg od or 40 mg bid followed by 3 weeks of esomeprazole 40 mg od or placebo. A responder after 4 weeks was a patient whose sum of symptom scores during the last 7 days was 0 or 1.

2. To compare the proportions of responders after the 8-week treatment period in the subgroup of responders after the 1-week test. The treatment period included the 1-week test of esomeprazole 40 mg od or 40 mg bid followed by 7 weeks of esomeprazole 40 mg od or placebo. A responder after the 1-week test was a patient whose sum of symptom scores during the last 3 days was 0 or 1.

3. To compare the proportions of responders after the 4-week treatment period in the subgroup of responders after the 1-week test. The treatment period included the 1-week test of esomeprazole 40 mg od or 40 mg bid followed by 3 weeks of esomeprazole 40 mg od or placebo.

4. To evaluate symptom response (ie, symptoms of pain or burning centred in the upper abdomen) to a 1-week placebo test as a tool for predicting responders at the end of an 8-week treatment period with placebo as a 1-week test followed by 7 weeks of esomeprazole 40 mg od or placebo.

5. To compare the proportions of responders after 4 and 8 weeks in the 2 subpopulations defined by the outcome of the 24-hour intra-esophageal pH-metry (normal/abnormal).

6. To evaluate the efficacy with regard to specific gastrointestinal (GI) symptoms after 4 and 8 weeks.

7. To compare the percentage of symptom-free days (ie, days without symptoms of pain or burning centred in the upper abdomen) during the 7-week treatment period for responders and non-responders after the 1-week test.

8. To compare the mean severity of symptoms of pain or burning centred in the upper abdomen during the 7-week treatment period for responders and non-responders after the 1-week test.

9. To compare the impact of treatment on aspects of health-related quality of life (HRQL) as measured by the dimensions sleep quality, emotions, and the ability to eat and drink what one likes, in the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire after 4 and 8 weeks of treatment.

10. To evaluate how anxiety, depression, and different GI symptom clusters at run-in predicted responders after 4 and 8 weeks of treatment by using the following Patient Reported Outcomes (PROs): the Hospital Anxiety and Depression Scale (HADSS), the Gastrointestinal Symptom Rating Scale (GSRS), and the Reflux Disease Questionnaire (RDQ).

11. To assess the burden of suffering from pain or burning centred in the upper abdomen as measured with the Short-Form 36 (SF-36) questionnaire.

12. To evaluate the safety and tolerability of esomeprazole 40 mg bid, 40 mg od, and placebo during a 1-week test for acid-related symptoms.

13. To evaluate the safety and tolerability of esomeprazole 40 mg od and placebo for 7 weeks in the treatment of upper GI symptoms.

Study design

The study comprised the following periods: a 2-week eligibility check, a 1-week run-in period, a 1-week test period of esomeprazole 40 mg od, esomeprazole 40 mg bid, or placebo, followed by a 7-week treatment period of esomeprazole 40 mg od or placebo. Both the 1-week test and 7-week treatment period were of a randomized, double-blind, placebo-controlled, and parallel-group design.

Target patient population and sample size

Patients with upper GI symptoms, (ie, symptoms of pain or burning centred in the upper abdomen) and normal findings at EGD. The patients were to be 18 to 70 years old, of either sex, and recruited through primary health-care centres or similar facilities. Both *Helicobacter pylori* (*H. pylori*) positive and negative patients were recruited.

The sample size was based on the comparison between esomeprazole 40 mg od and placebo regarding responders at the end of the 7-week treatment period in the subgroup of patients responding to the 1-week test with esomeprazole 40 mg od, 40 mg bid, or placebo. It was desirable to be able to show a difference in proportion of responders if the true difference was 15% or more.

Assuming response rates of 60% and 45% for esomeprazole 40 mg od and placebo, respectively, a total of 550 patients, randomized in the proportion 2:1, were needed for a significance level of 5% and a power of 90%.

As those who responded to the 1-week test were assumed to comprise 50% of the patients, and with an assumed rate of non-evaluable patients of 9%, a total of 1200 randomized patients were needed in the 2 active 1-week test groups. In order to also include a placebo 1-week arm for the evaluation of placebo as a tool for predicting responders after 7 weeks, an additional 300 patients were to be randomized, giving a total of 1500 randomized patients. The randomization was to give the proportions 2:2:1 between esomeprazole 40 mg od, 40 mg bid, and placebo during the 1-week test.

To further characterize the study population and to be able to exclude potential gastroesophageal reflux disease (GERD) patients from the analysis, a 24-hour intra-esophageal pH-metry test was performed in a subset of the population. The information was expressed as a 95% confidence interval for the proportion of potential GERD patients. If pH-metry was to be performed in 200 patients, the confidence interval would be of the type observed proportion ±7%, if the true proportion was around 50%. Another way to express this, is to say that the estimated proportion would have a standard error of 3.5%. (If the true proportion differed from 50%, the error would be smaller).

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

Investigational product

Esomeprazole tablets (as Nexium®) with 40 mg esomeprazole per tablet, administered orally (batch H 1365-01-02-02):

Nexium is trademark of the AstraZeneca group of companies.

- 1-week test period: esomeprazole 40 mg od or 40 mg bid.
- 7-week treatment period: esomeprazole 40 mg od.

Comparator

Placebo tablets for esomeprazole (identical in appearance), administered orally (batch H 1483-01-01-01):

- 1-week test period: placebo tablets administered od in the patient group that received esomeprazole 40 mg od, and bid in the patient group that received placebo.
- 7-week treatment period: placebo od.

Rescue medication

Antacid tablets with an acid-binding capacity of <16 mmol hydrochloric acid (HCl) were to be used as rescue medication on a *pro re nata* (*prn*) basis for the duration of the trial. Puchased locally in each country except for Sweden (batches H 0779-02-01-20 and H 0779-02-01-21), and Iceland (batch H 0779-02-01-22).

Duration of treatment

Eight weeks (1-week test + 7-week treatment period).

Criteria for evaluation (variables)

The full analysis set, ie, all randomized patients receiving investigational product (esomeprazole) or placebo, was used in the efficacy analyses. The safety analyses were based on all patients who took at least 1 dose of the investigational product/placebo and for whom data after randomization were available.

Efficacy and pharmacokinetics

Primary efficacy endpoint

The primary efficacy endpoint was based on symptom score recorded daily in the patient's diary. The patients judged their symptoms of pain or burning centred in the upper abdomen on a 4-graded scale:

- 0 = None
- 1 = Mild; awareness of symptoms, but easily tolerated

- 2 = Moderate; discomfort sufficient to cause interference with normal activities
- 3 = Severe; incapacitating, with inability to perform normal activities

The following definitions were used:

- The symptom response was the sum of symptom scores during the last 3 days of the 1-week test (ie, a number from 0 to 9).
- A responder to the 1-week test was a patient whose symptom response was 0 or 1.
- A responder after 8 weeks (4 weeks) was a patient whose sum of symptom scores over the last 7 days of the 8th week (4th week) was 0 or 1.

The primary efficacy endpoint was whether the patient was a responder or not after 8 weeks.

Seconday efficacy endpoints

The secondary efficacy endpoints were whether the patient was a responder or not after 4 weeks, the average symptom score and the percentage of symptom-free days during the 7-week treatment period, and presence/absence of specific GI symptoms after 4 and 8 weeks. The outcome of the 24-hour intra-esophageal pH-metry was used to define subpopulations (normal/abnormal) for additional analyses of the treatment effect.

Pharmacokinetics

The pharmacokinetics of esomeprazole was not investigated in this study.

Health-related quality of life

Primary PRO endpoint:

- The HRQL, as assessed by the QOLRAD dimensions sleep, food/drink, and emotions.

Explorative PRO endpoints:

- The RDQ for symptom evaluation and assessment of its diagnostic ability in identifying patients with acid-related upper GI symptoms.
- The satisfaction subscale of the Treatment Satisfaction Questionnaire (TSQ).

Health Economics

Explorative Health Economics (HE) endpoint:

- Assessment of productivity and activity loss due to acid-related upper GI symptoms using the Work Productivity and Activity Impairment (WPAI) questionnaire.

Safety

- The incidence, severity, and types of adverse events (AEs), including new or aggravated findings in physical examination.
- The incidence of clinically important changes in laboratory values, and in pulse and blood pressure (vital signs).

Statistical methods

Patients treated with either esomeprazole 40 mg od or 40 mg bid in the 1-week test and then with esomeprazole 40 mg od during the following 7-week treatment period were included in the evaluation of using the symptoms of pain or burning centred in the upper abdomen during a 1-week test as a tool for predicting responders at the end of the 7-week treatment period. The result was presented as the proportion of responders at the end of the 7-week treatment period as a function of the symptom response (0 to 9) at the end of the 1-week test. The 2 active treatment groups during the 1-week test were presented separately but also as pooled. Patients treated with placebo during the 1-week test and then continuing with esomeprazole 40 mg od during the following 7-week treatment period were analysed in the same way.

The difference between placebo and esomeprazole after the 7-week treatment period among the 1-week test responders were analysed by a chi-square test. Only patients responding to the 1-week test with esomeprazole 40 mg od or 40 mg bid were included in this analysis.

Adverse events were analysed by means of descriptive statistics and qualitative analysis. Incidence tables by system organ class (SOC) and preferred term were provided as well as patient listings. Results from objective safety measurements, ie, laboratory and vital signs values were analysed primarily by means of descriptive statistics.

All PROs were analysed descriptively and by standard statistical tests. They were also used in logistic regression analyses of responders after 4 and 8 weeks. The QOLRAD dimensions were analysed by analysis of variance (ANOVA), with the corresponding baseline value as covariates.

Patient population

Demography and baseline characteristics for the randomized population are presented in Table S1. Note that the population is presented based on the treatment during the test week.

Table S1 Patient population and disposition

		40 mg esomeprazole	80 mg esomeprazole	Placebo	Total
Population					
N randomized (N planned)		617 (600)	649 (600)	323 (300)	1589 (1500)
Demographic characteristics					
Sex (n and % of patients)	Male	192 (31%)	214 (33%)	115 (36%)	521 (33%)
	Female	425 (69%)	435 (67%)	208 (64%)	1068 (67%)
Age (years)	Mean	40.0	40.4	41.6	40.5
	Range	18-70	18-70	18-75	18-75
Race (n and % of patients)	Caucasian	539 (87%)	576 (89%)	282 (87%)	1397 (88%)
	Black	27 (4%)	18 (3%)	9 (3%)	54 (3%)
	Oriental	35 (6%)	38 (6%)	20 (6%)	93 (6%)
	Other	16 (3%)	17 (3%)	12 (4%)	45 (3%)
Baseline characteristics					
History of GI disease (months)	Median	12	12	12	12
	Range	3-99	3-99	3-99	3-99
Urea breath test (UBT)					
	-Negative	409 (69%)	428 (68%)	191 (61%)	1028 (67%)
	-Positive	188 (31%)	205 (32%)	121 (39%)	514 (33%)
pH monitoring results					
	-Abnor-mal	39 (76%)	43 (67%)	16 (59%)	98 (69%)
	-Normal	12 (24%)	21 (33%)	11 (41%)	44 (31%)
Symptom score sum during the last 7 days	Mean	9.7	9.7	9.7	9.7
	Range	2-21	3-21	4-21	2-21

(Continued)

Table S1 Patient population and disposition

		40 mg esomeprazole	80 mg esomeprazole	Placebo	Total
Symptom score sum during the last 3 days	Mean	4.3	4.2	4.3	4.2
	Range	0-9	0-9	0-9	0-9
Disposition					
N (%) of patients who	Com-pleted	544 (88%)	569 (88%)	289 (89%)	1402[a](88%)
	Discon-tinued	71 (12%)	79 (12%)	33 (10%)	183[a](12%)
	Not treated or no data on treatment	2 (0.3%)	1 (0.2%)	1 (0.3%)	4[a](0.3%)
N analysed for safety[b]		615	648	322	1585
N analysed for efficacy (ITT)		617	649	323	1589
N analysed for efficacy (PP)		NA	NA	NA	NA

a The number refers to the entire 8-week treatment period.

b Number of patients 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 and pharmacokinetic results

The pharmacokinetics of esomeprazole was not investigated in this study.

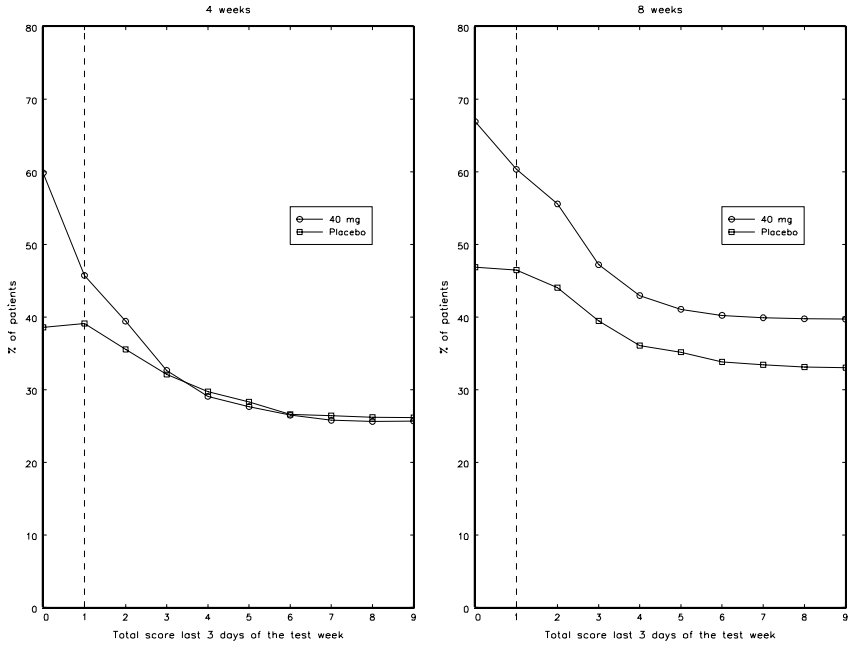
Efficacy

The percentages of responders after 4 and 8 weeks of treatment for the different possible definitions of a test-week responder are shown in Table S2 and Figure S1. The underlined test score sum of 1 highlights the definition given in secondary objective no. 2, ie, the case when a test-week responder is one whose score sum is at most 1.

Table S2 Responders after 4 and 8 weeks (40 mg or 80 mg in test week)

Test score sum	4 weeks					8 weeks				
	40 mg		Placebo			40 mg		Placebo		
	n	%	n	%	P-value	n	%	n	%	P-value
0	127	59.8	70	38.6	0.004	124	66.9	64	46.9	0.008
1	234	**45.7**	133	**39.1**	0.218	227	**60.4**	127	**46.5**	0.012
2	340	39.4	166	35.5	0.400	331	55.6	159	44.0	0.016
3	508	32.7	240	32.1	0.871	487	47.2	228	39.5	0.052
4	619	29.1	296	29.7	0.840	596	43.0	277	36.1	0.055
5	683	27.7	332	28.3	0.831	655	41.1	310	35.2	0.079
6	732	26.5	357	26.6	0.970	701	40.2	334	33.8	0.048
7	756	25.8	367	26.4	0.819	724	39.9	344	33.4	0.041
8	765	25.6	370	26.2	0.830	732	39.8	347	33.1	0.036
9	779	25.7	371	26.1	0.864	743	39.7	348	33.0	0.034

Figure S1 **Response after 4 and 8 weeks of treatment (40 mg or 80 mg in test week)**



The overall efficacy results from this study are summarized as:

- A 1-week treatment test with esomeprazole 40 or 80 mg daily predicted symptom response (ie, pain or burning centred in the upper abdomen) after further 3 or 7 weeks of treatment with esomprazole 40 mg daily. (Refers to the primary objective and the secondary objective no. 1.)

- Esomeprazole had a better effect in patients who responded to esomeprazole during the test week compared with placebo at 8 weeks: 60% of the test responders were still responders after a further 7 weeks of esomeprazole treatment, while the corresponding number for subsequent placebo treatment was 46% (see right-hand panel of Table S2). (Refers to the secondary objective no. 2.)

- There was a numerical, but no statistically significant difference in effect between esomeprazole and placebo at 4 weeks in the patients who responded to esomeprazole during the test week: 46% of the test responders were still

responders after a further 3 weeks of esomeprazole treatment, while the corresponding number for subsequent placebo treatment was 39% (see left-hand panel of Table S2). (Refers to the secondary objective no. 3.)

- Placebo as a test did not predict treatment response to esomeprazole. (Refers to the secondary objective no. 4.)
- There was no evidence for any difference between the proportion of responders at 4 and 8 weeks comparing the subpopulations having normal or abnormal outcome from the 24h intra-esophageal pH metry. (Refers to the secondary objective no. 5.)
- After 4 weeks, there were statistically significant differences in favour of esomeprazole in heartburn, discomfort centered in the upper abdomen and regurgitation. After 8 weeks, there were statistically significant differences in heartburn, vomiting, and regurgitation. (Refers to the secondary objective no. 6.)
- The proportion of symptom-free days (ie, days without symptoms of pain or burning centred in the upper abdomen) during the 7 weeks with active treatment was greater for the 1-week test responders than for non-responders. (Refers to the secondary objective no. 7.)
- The mean severity of symptoms (ie, pain or burning centred in the upper abdomen) during the 7 weeks with active treatment was lower for the 1-week test responders than for non-responders. (Refers to the secondary objective no. 8.)

Health-related quality of life

The PRO is summarized as:

- Esomeprazole improved the ability to eat and drink what one likes compared with placebo after 4 and 8 weeks of treatment among test responders. Esomeprazole also improved emotions after 8 weeks of treatment. There was no difference between esomeprazole and placebo regarding sleep quality. (Refers to the secondary objective no. 9.)
- The more pronounced anxiety, depression, and GI symptoms at run-in, the lower was the likelihood that a patient was a treatment responder. (Refers to the secondary objective no. 10.)
- The burden of illness in patients with upper GI symptoms and normal endoscopic findings was high, indicated by low scores in all dimensions of the SF-36 except physical functioning, as compared with a normative population. The most

profound difference was shown in the bodily pain dimension. (Refers to the secondary objective no. 11.)

Safety results

Table S3 Number (%) of patients who had at least 1 adverse event (AE) in any category, and total numbers of AEs (safety analysis set) during the test week

Category of AE	N (%) of patients who had an AE in each category[a]		
	40 mg (n=615)	**80 mg (n=648)**	**Placebo (n=322)**
Any AEs	132 (21%)	169 (26%)	76 (24%)
Serious adverse events (SAEs)	1 (<0.5%)	1 (<0.5%)	0
SAE leading to death	0	0	0
SAE not leading to death	1 (<0.5%)	1 (1%)	0
Discontinuations of study treatment due to adverse events	5 (1%)	7 (1%)	2 (1%)
Other significant adverse events (OAEs)	0	0	0
Total numbers of adverse events			
AEs	**181**	**240**	**126**
SAEs	**1**	**1**	**0**
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 1 category are counted once in each of those categories.

Table S4 **Number (%) of patients who had at least 1 adverse event (AE) in any category, and total numbers of AEs (safety analysis set) during the 7-week treatment period**

Category of AE	N (%) of patients who had an AE in each category[a]	
	40 mg (n=1020)	**Placebo (n=504)**
Any AEs	460 (45%)	225 (45%)
Serious adverse events (SAEs)	7 (1%)	5 (1%)
SAE leading to death	0	1(<0.5%)
SAE not leading to death	7 (1%)	4 (1%)
Discontinuations of study treatment due to adverse events	24 (2%)	20 (4%)
Other significant adverse events (OAEs)	0	0
Total numbers of adverse events		
AEs	**952**	**464**
SAEs	**9**	**6**
OAEs	**0**	**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.

The number of reported serious adverse events (SAEs) was low. There was 1 death reported (*lung cancer metastatic*): a patient treated with placebo, both during the test week and during the treatment period. Three SAEs were considered to be related to study treatment according to the reporting investigator. The non-serious AEs were mostly of mild or moderate intensity throughout the study and reported with similar frequency in the different treatment groups. There were no relevant clinical findings in haematology, clinical chemistry, or vital signs. To conclude, treatment with esomeprazole was well tolerated and did not raise any safety concerns.