Drug Product	Nexium®	**SYNOPSIS**	
Drug Substance	Esomeprazole		
Edition Number	1		
Study Code	SD-NED-0022		
Date	25 October 2005		

Supportive Test for Acid-Related Symptoms (STARS II) with esomeprazole and a following 7-week, double-blind, randomized, placebo controlled treatment period in uninvestigated patients with upper gastrointestinal symptoms

Study centre(s)

This study was conducted in 10 countries (129 centres): Austria (6 centres), Belgium (12 centres), Canada (42 centres), Finland (11 centres), France (16 centres), Hungary (5 centres), Mexico (11 centres), Norway (12 centres), South Africa (10 centres), and Switzerland (4 centres).

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: 16 December 2002

Last patient completed: 11 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 a "real life" patient population from primary health-care centres or similar facilities. 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 the efficacy with regard to specific gastrointestinal (GI) symptoms after 4 and 8 weeks.

5. 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.

6. 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.

7. 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.

8. 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 Dyspepsia Scale (HADS), the Gastrointestinal Symptom Rating Scale (GSRS), and the Reflux Disease Questionnaire (RDQ).

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

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

11. To evaluate the safety and tolerability of esomeprazole 40 mg od and placebo for 7 week in the treatment of upper gastrointestinal symptoms.

Study design

The study comprised the following periods: a 1-week run-in period, a 1-week test period of esomeprazole 40 mg od or esomeprazole 40 mg bid, 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

The target patient population was uninvestigated patients with upper GI symptoms, ie, pain or burning centred in the upper abdomen. The patients were to be 18 to 50 years, of either sex, and recruited through primary health-care centres or similar facilities. The patients had to be *Helicobacter pylori* (*H. pylori*) negative and patients with confirmed gastroesophageal reflux disease (GERD) were excluded.
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 or 40 mg bid. 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 proportions of 2:1, were needed for a significance level of 5% and a power of 90%.

As those who responded to the test week 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 for the 1-week test period.

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):

- 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 were administered od in the patient group that received esomeprazole 40 mg od
- 7-week treatment period: placebo od

Rescue medication

Rescue medication, ie, antacid tablets with an acid-binding capacity of <16 mmol hydrochlorid acid (HCl), was provided throughout the study. The patients were instructed to use the rescue medication on a *pro re nata (prn)* basis for the duration of the trial. The rescue medication was purchased locally in each country except for Finland (as Novalucol™ Novum tablets) (batch H 0779-02-01–20).

Nexium is a trademark of the AstraZeneca group of companies.

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 from 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.

Secondary 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.

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 type 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 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 with the 1-week test were presented separately but also as pooled.

The difference between placebo and esomeprazole after the 7-week treatment period among the 1-week test responders was 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 of treatment. 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	Total
Population				
N randomized (N planned)		621(600)	629 (600)	1250 (1200)
Demographic characteristics				
Sex (n and % of patients)	Male	264 (43%)	251 (40%)	515 (41%)
	Female	357 (57%)	378 60%)	735 (59%)
Age (years)	Mean	35.1	35.4	35.3
	Range	18-50	18-57	18-57
Race (n and % of patients)	Caucasian	596 (96%)	605 (96%)	1201 (96%)
	Black	13 (2%)	13 (2%)	26 (2%)
	Oriental	8 (1%)	8 (1%)	16 (1%)
	Other	4 (0.6%)	3 (0.5%)	7 (0.6%)
History of GI disease (months)	Median	12	12	12
	Range	3-99	3-99	3-99

(Continued)

Table S1 Patient population and disposition

		40 mg esomeprazole	80 mg esomeprazole	Total
Symptoms sum score during the last 7 days	Mean	9.8	9.6	9.7
	Range	2-21	2-21	2-21
Symptoms sum score during the last 3 days	Mean	4.3	4.3	4.3
	Range	0-9	1-9	0-9
Disposition				
N (%) of patients who	Completed	541 (87%)	553 (88%)	1094[a] (88%)
	Discontinued	79 (13%)	74 (12%)	153[a] (12%)
	Not treated or no data on treatment	1 (0.2%)	2 (0.3%)	3[a] (0.2%)
N analysed for safety[b]		620	627	1247
N analysed for efficacy (ITT)		621	629	1250
N analysed for efficacy (PP)		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 investigational product or placebo 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.

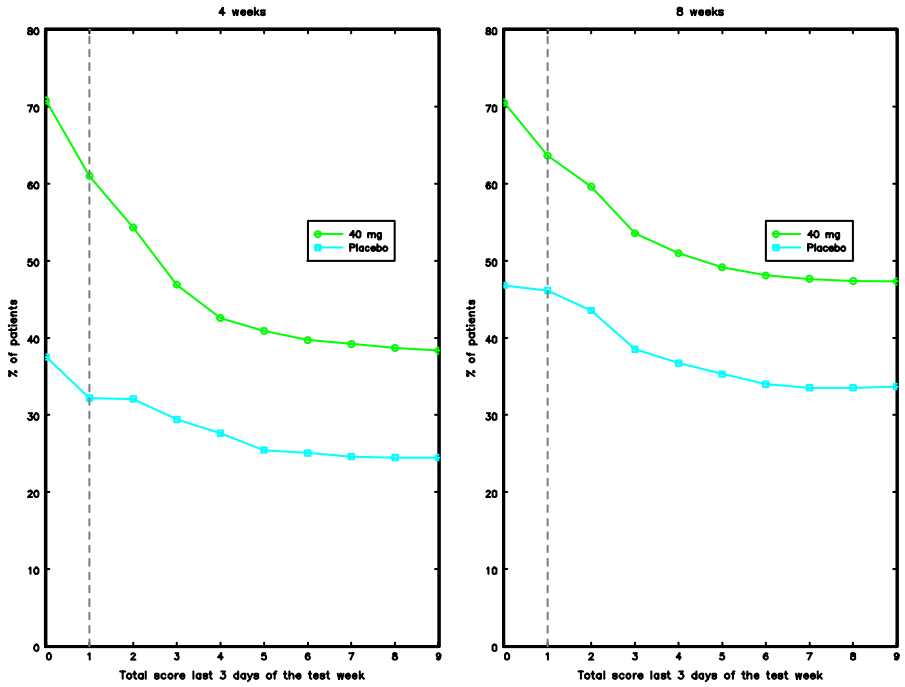
Efficacy results

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 of treatment

Test score sum	4 weeks					8 weeks				
	40 mg		Placebo			40 mg		Placebo		
	n	%	n	%	P-value	n	%	n	%	P-value
0	202	70.8	96	37.5	<0.001	197	70.6	94	46.8	<0.001
1	318	**61.0**	146	**32.2**	<0.001	311	**63.7**	143	**46.2**	<0.001
2	418	54.3	184	32.1	<0.001	411	59.6	179	43.6	<0.001
3	533	46.9	258	29.5	<0.001	517	53.6	249	38.6	<0.001
4	620	42.6	297	27.6	<0.001	604	51.0	286	36.7	<0.001
5	670	40.9	334	25.4	<0.001	653	49.2	323	35.3	<0.001
6	705	39.7	355	25.1	<0.001	686	48.1	344	34.0	<0.001
7	719	39.2	370	24.6	<0.001	699	47.6	358	33.5	<0.001
8	729	38.7	376	24.5	<0.001	707	47.4	364	33.5	<0.001
9	738	38.3	380	24.5	<0.001	716	47.3	368	33.7	<0.001

Figure S1 Response after 4 and 8 weeks of treatment



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 esomeprazole 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: 64% of the test responders were still responders after further 7 weeks of esomeprazole treatment, while the corresponding number for subsequent placebo treatment was 46% (see right panel of Table S2). (Refers to the secondary objective no. 2.)

- Esomeprazole had a better effect in patients who responded to esomeprazole during the test week compared with placebo at 4 weeks: 61% of the test responders

were still responders after further 3 weeks of esomeprazole treatment, while the corresponding number for subsequent placebo treatment was 32% (see left panel of Table S2). (Refers to the secondary objective no. 3.)

- Esomeprazole reduced all specified GI symptoms after 4 weeks of treatment, with a statistically significant difference compared with placebo for all symptoms except nausea and vomiting. After 8 weeks of treatment, the symptoms remained on the lowered level. (Refers to the secondary objective no. 4.)

- 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. 5.)

- 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. 6.)

Health-related quality of life

The PRO is summarized as:

- Esomeprazole improved sleep quality, emotions, and the ability to eat and drink what one likes compared with placebo after 4 and 8 weeks of treatment among test responders. (Refers to the secondary objective no. 7.)

- 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. 8.)

- The burden of illness in uninvestigated patients with upper GI symptoms 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. 9.)

Safety results

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

Category of AE	N (%) of patients who had an AE in each category[a]	
	40 mg N=620	**80 mg n=627**
Any AEs	124 (20%)	139 (22%)
Serious adverse events (SAEs)	1 (<0.5%)	5 (1%)
SAE leading to death	0	0
SAE not leading to death	1 (<0.5%)	5 (1%)
Discontinuations of study treatment due to adverse events	9 (1%)	4 (1%)
Other significant adverse events (OAEs)	0	0
Total numbers of adverse events)		
AEs	**173**	**207**
SAEs	**1**	**5**
OAEs	**0**	**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 in each of these categories.

Table S4 **Number (%) of patients who had at least 1 adverse event (AE) in any category, and total numbers of AE (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=773	**Placebo n=407**
Any AEs	284 (37%)	168 (41%)
Serious adverse events (SAEs)	4 (1%)	3 (1%)
SAE leading to death	0	0
SAE not leading to death	4 (1%)	3 (1%)
Discontinuations of study treatment due to adverse events	17 (2%)	16 (4%)
Other significant adverse events (OAEs)	0	0
Total numbers of adverse events		
AEs	**565**	**343**
SAEs	**6**	**7**
OAEs	**0**	**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 in each of these categories.

No death occurred during the study. There were few SAEs reported of which 3 were considered causally 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. The most commonly reported non-serious AEs were from the SOCs “Gastrointestinal Disorders”, “Infections And Infestations”, and “Nervous System Disorders”. The dominating events on a preferred-term level were *headache*, followed by symptoms from the GI tract, such as *diarrhoea*, *nausea*, *abdominal pain*, *abdominal distension*, and *vomiting*. There were no clinically relevant findings in physical examination, vital signs, haematology, or clinical chemistry during the study. To conclude, treatment with esomeprazole was well tolerated and did not raise any safety concerns.