Drug Product		**SYNOPSIS**	
Drug Substance(s)	Esomeprazole		
Study Code	D9914C00001		
Date	12 September 2006		

A Randomized Double-Blind Placebo-Controlled Multi-Centre Pilot Study to Assess Symptom Response in Subjects with Pain or Discomfort in the Chest Receiving Oral Treatment with Esomeprazole 40 mg bid for 4 weeks

Study centre(s)

This was a multicentre study with 49 centres in 4 countries: Canada, 17 centres; Denmark, 12 centres; Norway, 8 centres; and the Netherlands, 12 centres.

Publications

No publications based on this report have been made prior to the date of the report.

Study dates		**Phase of development**
First patient enrolled	27 May 2004	Phase IIIB
Last patient completed	29 July 2005	

Objectives

Primary objective:

The primary objective of this study was to compare esomeprazole 40 mg twice a day (bid) with placebo in relief of pain or discomfort in the chest after 4 weeks of treatment**,** where relief of pain or discomfort in the chest was defined as no more than 1 day with minimal symptoms during the last 7 days according to diary cards.

Secondary objectives:

1. To evaluate symptom response to esomeprazole during the first week, (ie, symptoms of pain or discomfort in the chest during the last 5 days of the first week) as a tool for predicting relief of pain or discomfort in the chest at the end of 4 weeks of treatment.

2. To evaluate the efficacy of esomeprazole with regard to investigator's question on overall pain or discomfort problems in the chest after 1 and 4 weeks of treatment.

3. To evaluate the safety and tolerability of esomeprazole 40 mg bid.

4. To evaluate the impact of treatment with esomeprazole on the severity of pain or discomfort in the chest as measured by the short form McGill pain questionnaire (MPQ) and by the short form Brief Pain Inventory (BPI) after 4 weeks of treatment.

5. To evaluate the impact of treatment with esomeprazole on Health Related Quality of Life (HRQL) as measured by the Quality of Life in Reflux And Dyspepsia (QOLRAD) questionnaire (chest pain version) after 4 weeks of treatment.

6. To assess the burden of suffering from pain or discomfort in the chest as measured with the standard version of the Short Form-36 (SF-36) at baseline for descriptive purposes.

7. To assess the degree of anxiety and/or depression at baseline as measured with the Hospital Anxiety and Depression (HAD) scale and to evaluate whether anxiety and/or depression have any association with relief of pain or discomfort in the chest.

8. To assess reflux symptoms as measured with the Reflux Disease Questionnaire (RDQ) at baseline.

9. To evaluate the efficacy of esomeprazole with regard to the Overall Treatment Evaluation (OTE) after 1 and 4 weeks.

Study design

This was a 4-week, randomized, stratified, double-blind, parallel-group, placebo-controlled, multi-centre study. Patients were first stratified in equal proportions into 1 of the following 2 strata:

Stratum 1: Patients who had acid-related symptoms, ie, heartburn or regurgitation of, on average, **at most** 1 day/week

Stratum 2: Patients who had acid-related symptoms, ie, heartburn or regurgitation of, on average, **at least** 2 days/week

and thereafter randomized in equal proportions to either esomeprazole 40 mg tablets bid or matching placebo for 4 weeks.

Target patient population and sample size

Patients with pain or discomfort in the chest as the primary reason for seeking care

- with a history of pain or discomfort in the chest at least the last 2 weeks and
- with at least 2 days of at least moderate symptoms of pain or discomfort in the chest during the last 7 days.

The patients were to be 18-70 years, of either sex, and recruited through primary medical care settings or similar facilities.

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

Esomeprazole tablets (as NEXIUM™) with 40 mg per tablet administered orally (batch numbers H 1365-01-02-03 and H 1365-01-02-04).

Matching placebo for esomeprazole tablets, administered orally (batch number H 1483-01-01-02).

Duration of treatment

4 weeks

Criteria for evaluation (main variables)

Efficacy

Primary outcome variable: Relief of pain or discomfort in the chest during the last week of the 4-week treatment. Relief of pain or discomfort in the chest was defined as no more than 1 day with minimal symptoms during the last 7 days according to the patient-assessed diary cards.

Secondary outcome variables:

- Symptom response during the first week based on diary cards, Days 3-7.
- The investigator's overall assessment of pain or discomfort in the chest during the first and fourth week
- Scores from the patient reported outcome (PRO) instruments measuring pain, Health Related Quality of Life (HRQL), anxiety and depression, health status, reflux-related symptoms, and overall treatment evaluation.

Pharmacokinetics and Health economics were not investigated in this study.

Safety

Standard safety assessments included adverse event reports, clinical laboratory data (haematology, serum chemistry, and urinalysis), vital signs, and physical examination.

Statistical methods

The primary variable, relief of pain or discomfort in the chest at the 4-week visit, was analysed within each stratum (1 and 2) by a Mantel-Haenszel test with stratification based on the baseline overall severity of pain or discomfort in the chest assessed by the investigator (ie, with the baseline severity as a factor). The investigator's overall assessment of pain or discomfort in the chest at 1 and 4 weeks was analysed in the same way. The predictive value of the symptom response during the first week was evaluated by descriptive statistics and by illustrating and comparing different symptom responses in Receiver Operating Characteristic Curves (ROCs). The MPQ VAS scale, the BPI scale, and each dimension of QOLRAD were analysed using an ANCOVA with the baseline assessment used as a covariate.

The primary variable was analysed for both the intention-to-treat (ITT) and the per-protocol (PP) populations and the secondary variables only for the ITT population. The 2 strata of patients were analysed separately.

Adverse events, clinical laboratory tests, and vital signs are presented using descriptive statistics for the safety population.

Patient population

The demographic characteristics of the study population are described in Table S1.

Table S1 Patient population and disposition

		Esomeprazole	Placebo	Total
Population				
N randomized (Stratum 1)		154	168	326
N randomized (Stratum 2)		152	147	299
Demographic characteristics (Stratum 1, ITT population)				
Gender (n and % of patients)	Male	80 (52)	85 (53)	165 (53)
	Female	73 (48)	76 (47)	149 (47)
Age (years)	Mean	46.8	46.4	46.6
	Range	18 to 76	21 to 72	18 to 76
Race (n and % of patients)	Caucasian	142 (93)	151 (94)	293 (93)
	Black	3 (2)	7 (4)	10 (3)
	Oriental	7 (5)	3 (2)	10 (3)
	Other	1 (1)	0 (0)	1 (<0.5)
Demographic characteristics (Stratum 2, ITT population)				
Gender (n and % of patients)	Male	75 (52)	76 (54)	151 (53)
	Female	69 (48)	65 (46)	134 (47)
Age (years)	Mean	46.7	47.9	47.3
	Range	18 to 73	19 to 72	18 to 73
Race (n and % of patients)	Caucasian	135 (94)	135 (96)	270 (95)
	Black	5 (3)	4 (3)	9 (3)
	Oriental	4 (3)	2 (1)	6 (2)
	Other	0 (0)	0 (0)	0 (0)
Baseline characteristics (Stratum 1, ITT population)				
BMI (kg/m2)	Mean	27.2	27.0	27.1
	Range	19 to 56	17 to 43	17 to 56
Current smoker? (n and % of patients)				
	No	104 (68)	113 (70)	217 (69)
	Yes	49 (32)	48 (30)	97 (31)

Table S1 Patient population and disposition

		Esomeprazole	Placebo	Total
Other current nicotine intake?				
	No	150 (98)	161 (100)	311 (99)
	Yes	3 (2)	0 (0)	3 (1)
Severity of overall pain or discomfort in the chest	Mean	3.1	3.1	3.1
	Range	1.0 to 5.0	1.0 to 6.0	1.0 to 6.0
Days with symptoms of pain or discomfort in the chest[a]	Mean	4.7	4.8	4.8
	Range	1.0 to 7.0	1.0 to 7.0	1.0 to 7.0
Baseline characteristics (Stratum 2, ITT population)				
BMI (kg/m2)	Mean	27.8	28.2	28.0
	Range	19 to 53	19 to 42	19 to 53
Current smoker?				
	No	99 (69)	94 (67)	193 (68)
	Yes	45 (31)	47 (33)	92 (32)
Other current nicotine intake?				
	No	138 (98)	138 (98)	276 (97)
	Yes	6 (4)	2 (1)	8 (3)
Severity of overall pain or discomfort in the chest	Mean	3.3	3.2	3.3
	Range	1.0 to 5.0	1.0 to 6.0	1.0 to 6.0
Days with symptoms of pain or discomfort in the chest[a]	Mean	4.9	4.9	4.9
	Range	2.0 to 7.0	2.0 to 7.0	2.0 to 7.0
Disposition (Stratum 1)				
N (%) of patients who	Completed	124	139	263
	Discontinued	33	27	60
N analysed for safety[b]		157	166	323
N analysed for efficacy (ITT)		153	161	314
N analysed for efficacy (PP)		99	104	203
Disposition (Stratum 2)				
N (%) of patients who	Completed	119	117	236
	Discontinued	29	29	58

Table S1 Patient population and disposition

	Esomeprazole	Placebo	Total
N analysed for safety[b]	148	146	294
N analysed for efficacy (ITT)	144	141	285
N analysed for efficacy (PP)	101	92	193

[a] Last week before entry into the study.

[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 results

The overall percentage of patients with symptom relief after 4 weeks in Stratum 1 was 38.7% in the esomeprazole group and 25.5% in the placebo group. The difference is statistically significant (p=0.018). The corresponding values in Stratum 2 were 27.2% and 24.2%, respectively (p=0.541)

For the responses during the last 5 days of the first treatment week used as predictors of relief after 4 weeks, negative predictive values were 84% at a score sum of 4 in Stratum 1, and 89% at a score sum of 5 in Stratum 2. Corresponding positive predictive values were 68% and 51%, respectively.

After esomeprazole treatment, self-reported pain (based on the McGill Visual Analogue scale) was significantly reduced and the patient's quality of life was significantly improved compared to placebo in the sleep and physical dimensions of QOLRAD for patients in Stratum 1, but otherwise no clear treatment benefit could be seen by the evaluation of the PRO forms.

The results for the primary efficacy objective are summarized in Table S2.

Table S2 Relief (overall severity) after 4 weeks (ITT population)

	Esomeprazole		Placebo			
	n	%	n	%	Difference	p-value
Stratum 1	142	38.7	153	25.5	13.2	0.018
Stratum 2	136	27.2	132	24.2	3.0	0.541

Safety results

In this primary care population of patients with undiagnosed pain or discomfort in the chest, esomeprazole 40 mg bid was well tolerated and no safety concerns were raised. AEs were reported by a higher number of patients in the esomeprazole group than in the placebo group (37% vs 30%). The most frequently reported AEs were in the gastrointestinal disorders SOC,

the infections and infestations SOC, and the nervous system disorders SOC. The most frequently reported AEs were headache, diarrhea, and nausea. There were few AEs in the cardiac disorders SOC: 1.0% (3) in the placebo group (myocardial infarction, left bundle branch block, and palpitations) and none in the esomeprazole group).

Overall, few SAEs were reported (1%). None of the SAEs was causally related to study treatment. Adverse events leading to discontinuation of study treatment (DAEs) were reported by 3% of patients in each treatment group. The most commonly reported DAEs occurred in the GI disorders organ class and were reported with similar frequency (2%) by patients in both treatment groups. No deaths occurred during this study and no event was classified as an OAE.

There were no clinically relevant trends in either treatment group with regard to laboratory variables, physical examinations, or vital signs. Isolated changes both within and outside the laboratory reference ranges were observed for most of the laboratory variables. These findings did not raise any safety concerns.

Adverse events are summarized in Table S3 and the most commonly reported adverse events are presented in Table S4.

Table S3 Number (%) of patients who had an adverse event in any category[a], and total numbers of adverse events (Safety population)

Category of adverse event	Esomeprazole n=305	Placebo n=312	All n=617
Any adverse events	113 (37)	95 (30)	208 (34)
Serious adverse events	3 (1)	3 (1)	6 (1)
Serious adverse events leading to death	0 (0)	0 (0)	0 (0)
Discontinuations of study treatment due to adverse events	10 (3)	9 (3)	19 (3)
Other significant adverse event	0 (0)	0 (0)	0 (0)
	Total number of adverse events		
Any adverse events	177	139	316
Deaths	0	0	0
Serious adverse events	3	3	6
Other significant adverse events	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 Adverse events by preferred term. Number (%) of patients with the most frequently reported AEs, sorted by decreasing order of frequency[a] (Safety population)

Preferred term	Esomeprazole n=305	Placebo n=312	All n=617
Headache	15 (4.9)	18 (5.8)	33 (5.3)
Diarrhoea	8 (2.6)	11 (3.5)	19 (3.1)
Nausea	11 (3.6)	7 (2.2)	18 (2.9)
Back pain	6 (2.0)	7 (2.2)	13 (2.1)
Constipation	7 (2.3)	5 (1.6)	12 (1.9)
Dizziness	4 (1.3)	6 (1.9)	10 (1.6)
Abdominal pain	5 (1.6)	4 (1.3)	9 (1.5)
Nasopharyngitis	5 (1.6)	3 (1.0)	8 (1.3)
Influenza	4 (1.3)	4 (1.3)	8 (1.3)
Dyspepsia	2 (0.7)	5 (1.6)	7 (1.1)
Abdominal pain upper	2 (0.7)	5 (1.6)	7 (1.1)
Arthralgia	4 (1.3)	2 (0.6)	6 (1.0)
Bronchitis	2 (0.7)	3 (1.0)	5 (0.8)
Upper respiratory tract infection	5 (1.6)	0	5 (0.8)
Dry mouth	2 (0.7)	3 (1.0)	5 (0.8)
Myalgia	3 (1.0)	1 (0.3)	4 (0.6)
Flatulence	2 (0.7)	2 (0.6)	4 (0.6)
Cough	1 (0.3)	3 (1.0)	4 (0.6)
Gastroenteritis	4 (1.3)	0	4 (0.6)

[a] This table uses a cut-off of 1%

Date of the report
12 September 2006