AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	Esomeprazole
Study Code	D9612L00076
Edition Number	1
Date	30 October 2008

Development of an Algorithm for Identification of Responders to Short Term Treatment with Esomeprazole (Nexium®) in Primary Care

Study dates: First patient enrolled: 24 May 2006
Last patient completed: 07 November 2007

Phase of development: Therapeutic use (IV)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

The study was conducted at 59 Primary Care Physician centres in Denmark.

Publications

An abstract of the main study results was presented at the 2008 DDW in San Diego.

Objectives

Primary objective

The primary objective of the study was to develop, and test, an algorithm for identification of responders to empirical esomeprazole treatment in Primary Care.

Secondary objectives

The secondary objectives of the study were:

1. To evaluate the response rate (absence of the key complaint for the last 3 days of the treatment period (2 weeks +/- 2 days).

2. To compare time to response between esomeprazole and placebo. Time to response is defined as the first day of sustained absence of the key complaint.

3. To describe the key complaints.

4. To assess patient satisfaction.

5. To assess disease impact on quality of life and certain health economic parameters.

Study design

Double blind, randomised, placebo-controlled, multicentre, group comparison.

Target patient population and sample size

Patients were of either gender aged 18 years or above, who attended a Primary Care Physician due to symptoms suggestive of acid related disease and, according to normal routine, the Physician would have prescribed an acid-inhibiting agent.

The patients were asked to phrase in their own words the nature of the complaint, which caused the consultation, i.e. the key complaint. The key complaint was the variable by which the effect of esomeprazole or placebo was evaluated.

The algorithm should define at least 25% of the patients as non-responders. The analyses from a prior randomised trial would define 40% as non-responders if the therapeutic gain (the percentage of response in esomeprazole treated patients minus the percentage of response in placebo treated patients) of omeprazole was > 0. However the inclusion to the study was based on simple addition of symptoms, whereas the inclusion to the present study was based on the clinical evaluation of the Primary Care Physician, which had been shown to be more precise. Consequently the algorithm was expected to fulfill the criteria of defining at least 25% as non-responders. It was estimated that 800 patients were sufficient to develop the algorithm.

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

Esomeprazole tablets 40 mg (batch numbers H-1365-01-02-07 and H1365-01-02-05) once daily or matching placebo tablets (batch numbers H-1483-01-01-02 and H1483-01-01-02).

Duration of treatment

The duration of the treatment was 2 weeks.

Criteria for evaluation

Efficacy

Primary outcome variable

The primary outcome variable was the absence of the patient's key complaint in the last 24 hours of the 2-week treatment period.

Secondary outcome variables

1. Absence of key complaint during the last 3 days of the 2-week treatment period as an average for the last 3 days.

2. Time (in days) to response is defined as the first day of sustained absence of the key complaint (calculated from the date of Visit 1).

3. Key complaints at baseline and at the end of the treatment period. The key complaint was graded as:

    - None (only at the end of the treatment period)
    - Mild
    - Moderate
    - Severe

4. Patient satisfaction at the end of the treatment period

5. Patient Reported Outcomes

    Reflux Disease Questionnaire (RDQ)
    Description of study patient population using RDQ items and predefined RDQ dimensions (sub-scales).

    Categorisation of sub-populations with predominant GERD symptoms or predominant dyspepsia symptoms at baseline based upon the responses to RDQ.

Assessing in these categorised sub-populations, treatment –induced changes in responses to RDQ related to frequency and severity of symptoms from baseline to the end of the 2-week treatment period.

EuroQol – 5 Dimensions (EQ – 5D) Questionnaire
Assessing health state utilities from baseline to the end of the 2-week treatment period.

Work Productivity and Activity Impairment: Upper Gastrointestinal Symptoms (WPAI:UGIS) Questionnaire
Work productivity losses and reduced productivity while carrying out daily activities related to Upper Gastrointestinal Symptoms at baseline and at the end of the treatment period.

Work productivity losses included absence from work (*absenteeism*) (hours) plus reduced effectiveness (percent reduced productivity) while at work *(presenteeism)*.

Impact of Upper Gastrointestinal Symptoms on daily activities was expressed as percent reduced productivity while carrying out daily activities.

All the above-mentioned patient self-completed questionnaires were administered both at baseline and at the end of the treatment period, after patient's key complaint had been recorded.

Safety

Only Adverse Events that resulted in treatment discontinuation and Serious Adverse Events were recorded.

Statistical methods

To develop and validate a model for prediction of the primary response after 2 weeks of treatment, the patients were divided into two samples: a **model sample** (the first included 60% of the patients) and a **test sample** (the last included 40% of the patients).

In the model sample the association between the primary response variable and the descriptive variables including their possible dependence on (or "interaction" with) the therapy given (esomeprazole or placebo) was studied using logistic regression analysis. The analysis resulted in a logistic regression model for prediction of the response after 2 weeks of treatment. The model included both "prognostic" variables being associated with the response independently of the treatment (similar associations in esomeprazole and placebo groups) and "therapeutic" variables for which the association with the response differed significantly between the esomeprazole and placebo groups. The predictive value of the therapeutic index was tested in the independent patients in the **test sample** (the last 40%). For each of these patients the therapeutic index was calculated and the patients were classified into 3 groups according to the value of their therapeutic index. In each of the 3 groups the observed response in percent was recorded. The therapeutic gain (the percentage of response in

esomeprazole treated patients minus the percentage of response in placebo treated patients) was calculated in the 3 groups. Testing of difference in response was performed using Armitage's test for trend in proportions and Fisher's exact probability test. Difference in response rate was tested using the Chi-square test. Time to response was compared using the logrank test. Safety variables are presented using descriptive statistics.

Patient population

Patients of either gender, aged 18 years or above, who attended a Primary Care Physician due to symptoms suggestive of acid related disease and, according to normal routine, the Physician would prescribe an acid-inhibiting agent.

Table 1 Patient disposition

	Esomeprazole	Placebo
Disposition		
n randomized	422	413
n(%) of patients who completed	401(95.0)	378(91.5)
n(%) of patients who discontinued	21(5.0)	35(8.5)
n(%) analysed for safety[a]	415(99.7)	403(99.5)
n(%) analysed for efficacy (ITT[b])	410(97.2)	397(96.1)
n(%) analysed for efficacy (PP[c])	275(65.2)	268(64.9)

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
[b] TT=Intention-to-treat
[c] PP=Per-protocol

Table 2 Demographics and baseline characteristics (ITT population)

Baseline characteristics	Esomeprazole (n=410)	Placebo (n=397)
Gender, n(%)		
Male	189(46.1)	174(43.8)
Female	221(53.9)	223(56.2)
Race, n(%)		
Caucasian	407(99.3)	386(97.2)
Black	1(0.2)	1(0.3)
Oriental	2(0.5)	7(1.8)
Other	0(0.0)	3(0.8)
Age, years		
Mean(SD)	52(16)	52(15)
Min-Max	17-87	18-90
Weight, kg		
Mean(SD)	78.1 (16.3)	78.6(16.2)
Min-Max	41-132	36-130

Baseline characteristics	Esomeprazole (n=410)	Placebo (n=397)
Height, cm		
Mean(SD)	170.5(9.9)	171.8(9.3)
Min-Max	149-202	150-205
Nicotine use, n(%)	120(29.3)	113(28.5)
Alcohol use[a], n(%)	16(3.9)	30(5.0)
Duration of gastrointestinal symptoms, n(%)		
≤ 3 months	171(41.7)	168(42.3)
> 3 months and ≤ 12 months	81(19.8)	62(15.6)
> 12 months	158(38.5)	167(42.1)
Severity of key complaint, n(%)		
Mild	102(24.9)	116(29.2)
Moderate	224(54.6)	217(54.7)
Severe	82(20.0)	63(15.9)
Duration of key complaint, n(%)		
≤ 1 week	46(11.2)	51(12.8)
> 1 week to 1 month	158(38.5)	135(34.0)
> 1 month	206(50.2)	211(53.1)

[a] More than recommended by the Danish National Board of Health

Table 3 Frequency (n, %) of gastrointestinal specific symptoms during the past 3 days at baseline (ITT population)

Gastrointestinal specific symptoms	Esomeprazole (n=410)	Placebo (n=397)
PAIN		
Pain		
Present, but not bothersome	99(24.1)	107(27.0)
Bothersome	206(50.2)	193(48.6)
Very bothersome	57(13.9)	52(13.1)
Region		
Behind the chest bone	98(27.1)	112(31.8)
Epigastric region ("triangle")	214(59.1)	191(54.3)
Diffusely in the upper stomach	45(12.4)	48(13.6)
Other	5(1.4)	1(0.3)
Quality of the pain		
Burning, itching, sensation of acid	284(78.5)	259(73.6)
Shooting (like tooth pain)	98(27.1)	108(30.7)
Dull (sensation of stone)	109(30.1)	88(25.0)
Other	12(3.3)	17(4.8)

Gastrointestinal specific symptoms	Esomeprazole (n=410)	Placebo (n=397)
Dynamics		
Constant	92(25.4)	86(24.4)
Periodic	271(74.9)	273(77.6)
Pain during night	163(45.0)	181(51.4)
Pain during morning	182(50.3)	174(49.4)
Relieved by defecation or passage of flatus	42(11.6)	62(17.6)
Relieved by vomiting	26(7.2)	43(12.2)
Hunger pain	119(32.9)	113(32.1)
Postprandial pain	144(39.8)	137(38.9)
Relieved by food	163(45.0)	170(48.3)
Relieved by antacids	234(64.6)	229(65.1)
OTHER SYMPTOMS		
Heartburn		
Present, but not bothersome	106(25.9)	93(23.4)
Bothersome	143(34.9)	139(35.0)
Very bothersome	44(10.7)	42(10.6)
Regurgitation	258(62.9)	246(62.0)
Early satiety	122(29.8)	110(27.7)
Post-prandial fullness	137(33.4)	128(32.2)
Bloating	188(45.9)	186(46.9)
Belching	139(33.9)	144(36.3)
Nausea	141(34.4)	137(34.5)
Constipation	58(14.1)	46(11.6)
Loose stools, diarrhoea	66(16.1)	55(13.9)
Incomplete evacuation	61(14.9)	52(13.1)
Vomiting in the morning	21(5.1)	15(3.8)
Dysphagia	39(9.5)	38(9.6)

Summary of efficacy and patient-reported outcome (PRO) results

In the ITT-population absence of the patient's key complaint in the last 24 hours at the end of the 2-week treatment period was 68% in the esomeprazole group and 44 % in the placebo group ($p<0.00001$).

Development of the algorithm

To develop and validate the model for prediction of the primary response after 2 weeks of treatment, the patients were divided into two samples: 484 patients in the **model sample** and 321 patients in the **test sample**.

From the model sample a Therapeutic Index was developed to predict the therapeutic response (the difference between response to esomeprazole and placebo) using logistic regression analysis with backward elimination of insignificant variables among 41 descriptive patient-characteristics and symptoms. The validity of the index was tested in the test sample. In the

model sample the symptoms 'significant heartburn' and 'early satiety' was associated with an increase in the response to treatment with esomeprazole, whereas the symptoms 'dull pain', 'pain relieved by bowel movements' and 'nausea' in women were associated with a decrease in the response to esomeprazole.

By filling in the patient's symptoms into the Table below a simple calculation of the Therapeutic Index in an individual patient could be performed.

Table 4 Calculation of the Therapeutic Index for an individual patient

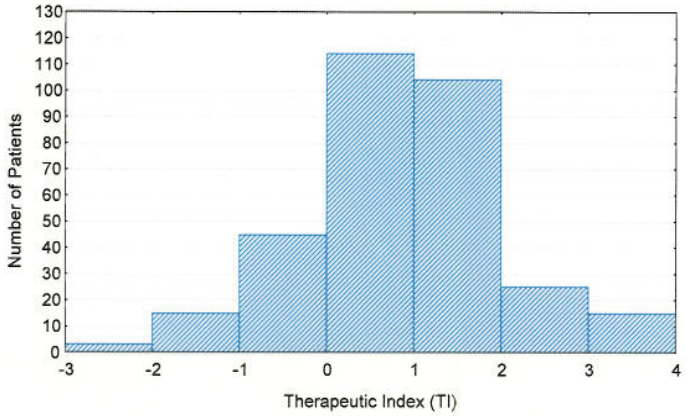
Presence of the symptom	**Yes**	**No**	**Score[a]**
Significant heartburn	+19	+9	
Early satiety	+12	0	
Dull pain quality	-14	0	
Pain relieved by bowel movement	-13	0	
Nausea in women	-9	0	
Therapeutic Index = SUM of the scores in the column 'Score' multiplied by 0.1 =			

[a] The score is the figure taken from the 'Yes' or the 'No' column for each of the five symptoms

Therapeutic index in the test sample

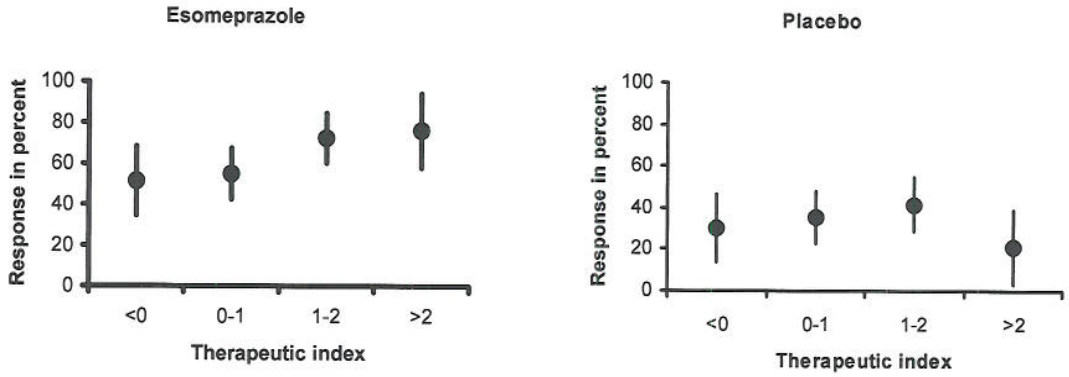
A Therapeutic Index was calculated for each patient in the test sample and the distribution of the Index is shown in Figure 1.

Figure 1 Therapeutic Index in the test sample (n=321)



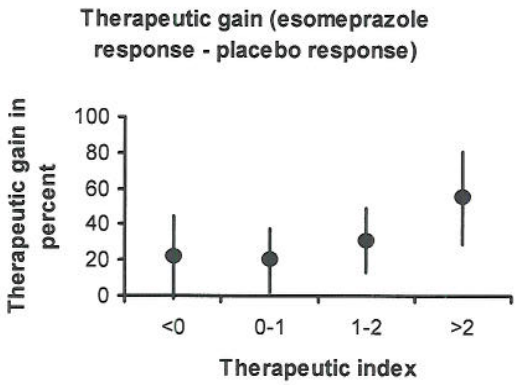
Response to treatment with esomeprazole and placebo by the calculated Therapeutic Index for patients in the test sample is shown in Figure 2.

Figure 2 Response to treatment by Therapeutic Index in the test sample (n=321)



The therapeutic gain (the percentage of response in esomeprazole treated patients minus the percentage of response in placebo treated patients) by the calculated Therapeutic Index for the patients in the test sample is shown in Figure 3.

Figure 3 Therapeutic gain by the calculated Therapeutic Index in the test sample (n=321)



Relations between the calculated score for the Therapeutic Index, grade of response and the therapeutic gain (the percentage of response in esomeprazole treated patients minus the percentage of response in placebo treated patients) could be described in the following way:

- Therapeutic Index <1: Low response: Therapeutic gain ~20% (0%-40%)
- Therapeutic Index 1-2: Intermediary response: Therapeutic gain: ~30% (15%-45%)
- Therapeutic Index >2: High response: Therapeutic gain ~50% (30%-70%)

By calculating a Therapeutic Index for an individual patient using Table 4 it is the possible to estimate the probability of response to treatment with esomeprazole in that patient. For clinical use, Table 4 could be transformed to a simple pocket card as a tool for calculating a Therapeutic Index.

Time to response

In the ITT-population the median time to response from baseline to the first day of sustained absence of the key complaint was 9 days in the esomeprazole group and 22 days in the placebo group (p<0.001).

Key complaint

The severity of the patient's key complaints at the end of the 2-week treatment period is shown in Table 5.

Table 5 Key complaints at the end of the treatment period (ITT population)

Key complaints	Esomeprazole (n=410)	Placebo (n=397)
Severity during the last 24 hours of the treatment period, n(%)		
None	280(68.3)	175(44.3)
Mild	70(17.1)	90(22.8)
Moderate	52(12.7)	105(26.6)
Severe	8(2.0)	25(6.3)
Severity during the last 3 days of the treatment period, n(%)		
None	252(61.5)	145(36.7)
Mild	92(22.4)	110(27.8)
Moderate	59(14.4)	113(28.6)
Severe	7(1.7)	27(6.8)

Patient satisfaction

In the ITT-population 65% of the patients in the esomeprazole group were satisfied with the treatment at the end of the study period. The corresponding figure for the placebo group was 40% (p<0.001).

Patient Reported Outcomes

Esomeprazole was found to be superior to placebo in all four dimensions in the Reflux

Disease Questionnaire (heartburn, aid regurgitations, dyspepsia, GERD (combines the symptoms 'Heartburn and 'Acid regurgitation')) with regards to both absolute and relative reduction in symptoms after 2 weeks of treatment. In addition, the number of patients with full removal of symptoms, i.e. –100% relative change is higher in the esomeprazole group compared to the placebo for all four dimensions in the questionnaire.

By using the 'EuroQol – 5 Dimension Questionnaire' (EQ-5D) a statistically significant difference was seen in favor of esomeprazole both regarding 'Time trade-off' and the 'Visual Analogue scale' when using Danish EQ-5D tariffs.

Furthermore, using the 'Work Productivity and Activity Impairment: Upper Gastrointestinal Symptoms (WPAI:UGIS) Questionnaire' it was shown, that esomeprazole was superior to placebo in reducing productivity variable scores, i.e. improving the work productivity.

Summary of safety results

In this study, only Adverse Events that resulted in treatment discontinuation and Serious Adverse Events were recorded. Number of patients who experienced an Adverse Event is described in Table 6.

Table 6 Number (%) of patients who had an adverse event in any category, and total numbers of adverse events (Safety population).

Category of adverse event[a]	Esomeprazole (n=415)	Placebo (n=403)
Any adverse event	6(1.4)	10(2.5)
Serious adverse event	3(0.7)	2(0.5)
Discontinuation of study treatment due to AE	5(1.2)	9(2.2)

[a] Patients with multiple events in the same category are only counted once in that category