AstraZeneca

Drug product:		**SYNOPSIS**	
Drug substance(s):	AZD0865 mesylate (AR-H044277AW)1)		
Document No.:	D9770C00011		
Edition No.:	1		
Study code:	D9770C00011		
Date:	13 December, 2005		

A 4-week, randomised, double-blind, multicentre, dose-finding Phase IIb study with AZD0865 25, 50, 75 mg and esomeprazole 20 mg, given orally once daily for the treatment of GERD without reflux (erosive) esophagitis according to the LA classification in adult patients

Study dates

First patient enrolled 13 May 2004

Last patient completed 27 April 2005

Phase of development

Therapeutic exploratory (II)

Objectives

The primary objective was:

- To compare the efficacy of AZD0865 25, 50 and 75 mg with respect to the time to sustained absence of patient-reported heartburn, ie, a burning feeling behind the

breastbone defined as the time to the first of 7 consecutive days free of heartburn, in patients with GERD without reflux[1] esophagitis according to the LA classification.

The secondary objectives were:

- To compare the efficacy of AZD0865 25, 50, 75 mg and esomeprazole 20 mg, with respect to each of the patient-reported symptoms: a burning feeling behind the breastbone (= definition of heartburn in this study), pain behind the breastbone, a burning feeling in the centre of the upper stomach, pain in the centre of the upper stomach, **an acid taste** in the mouth, and unpleasant movements of materials upwards from the stomach.

- To evaluate safety and tolerability during the treatment period by assessment of adverse events, laboratory variables, blood pressure (BP), pulse, electrocardiogram (ECG) and physical examination.

- Additional secondary objectives such as: efficacy of AZD0865 25, 50, 75 mg and esomeprazole 20 mg, with respect to investigator-reported symptoms, health-related quality of life assessed by the Quality of Life in Reflux and Dyspepsia (QOLRAD), regression of histological findings in distal esophagus, intraesophageal/intragastric pH as well as population pharmacokinetic properties of AZD0865, are presented in the full report.

Study design

This was a randomised, 4-arm, parallel group, double-blind, double-dummy, multicentre dose-finding study of 4 weeks duration.

Target patient population and sample size

Male and female patients, 18 to 70 years with GERD without reflux[1] esophagitis, ie, without esophageal mucosal breaks according to the Los Angeles (LA) classification. The patients had to identify their main symptom as heartburn defined as a burning feeling behind the breastbone. Approximately 300 evaluable patients per treatment group were required with an additional 10% to guard for drop-out; in total 1400 patients.

Statistical methods

The primary endpoint was addressed using a log rank test. The analysis of the secondary endpoints included standard statistical methods, such as Wilcoxon signed rank test for ordinal variables, t-test for continuous variables if appropriate and log rank tests for time to event variables. Observations in all variables including safety variables were summarised descriptively.

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[1] Terminology change from Clinical Study Protocol (erosive esophagitis) to Clinical Study Report (reflux esophagitis) to achieve consistency across all AZD0865 documentation.

Patient population

The study population is considered to be adequately representative of the target population, ie, patients with symptoms of GERD and without reflux esophagitis (no mucosal breaks according to the LA classification). Demographic characteristics (age, sex) and *Helicobacter pylori* prevalence were similar to that seen in previous clinical studies with esomeprazole.

Distribution of all patient characteristics was similar in all treatment arms.

Table S1 Patient population and disposition

		AZD0865 25 mg		AZD0865 50 mg		AZD0865 75 mg		Esomeprazole 20 mg	
Population									
n randomised (n planned)		364	(350)	360	(350)	368	(350)	377	(350)
Demographic characteristics									
Sex n (%)	Male	148	(40.8)	149	(41.5)	144	(39.8)	142	(37.8)
	Female	215	(59.2)	210	(58.5)	218	(60.2)	233	(62.1)
Age (years)	Mean (SD)	46.5	(13.1)	46.4	(12.7)	47.0	(13.0)	45.0	(12.7)
	Range	18-70		18-72		18-72		18-69	
Race n (%)	Caucasian	302	(83.2)	287	(79.9)	299	(82.6)	301	(80.3)
	Black	20	(5.5)	23	(6.4)	20	(5.5)	26	(6.9)
	Oriental	5	(1.4)	4	(1.1)	8	(2.2)	4	(1.1)
	Other	36	(9.9)	45	(12.5)	35	(9.7)	44	(11.7)
Baseline characteristics									
Helicobacter pylori, positive n (%)		56	(15.4)	71	(19.8)	70	(19.3)	79	(21.1)
Intensity of symptom: A burning feeling behind your breastbone, n (%)									
	None	0	(0)	0	(0)	1	(0.3)	0	(0)
	Mild	1	(0.3)	1	(0.3)	0	(0)	0	(0)
	Moderate	192	(52.9)	207	(57.8)	211	(58.3)	226	(60.3)
	Severe	156	(43.0)	147	(41.0)	144	(39. 8)	144	(38.4)
	Missing	14	(3.9)	4	(1.1)	6	(1.7)	5	(1.3)
Disposition									
n of patients who	completed	335		328		432		341	
	discontinued	29		32		44		36	

	AZD0865 25 mg	AZD0865 50 mg	AZD0865 75 mg	Esomeprazole 20 mg
n analysed for safety[a]	363	359	362	375
n analysed for efficacy (ITT)	363	359	362	375
n analysed for efficacy (PP)	258	256	268	281

[a] 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 time to sustained absence of a burning feeling behind the breastbone, defined as the time to the first of 7 consecutive days free of this symptom, was approximately 12 days for all treatments. The cumulative incidence is graphed in Figure S1 for daytime and night-time combined. No differences could be seen, at any time-point studied (at 1, 2 or 4 weeks), between the 3 doses of AZD0865 (ITT and PP). Neither could any consistent difference be observed for the 3 doses of AZD0865 in comparisons with esomeprazole 20 mg.

Figure S1 Cumulative incidence of sustained absence of a burning feeling behind the breastbone (day and night), ITT Population

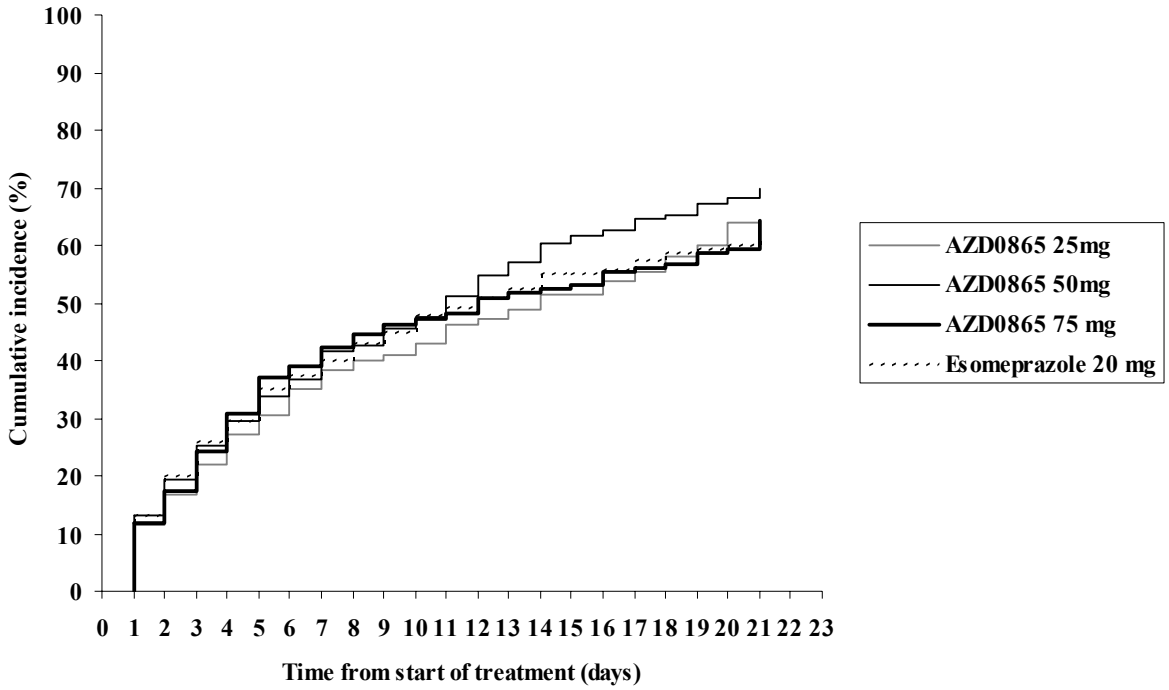

Table S2 Pairwise comparisons of treatments with respect to the cumulative incidence of sustained absence of a burning feeling behind the breastbone (day and night), ITT Population

Treatment comparison	p-value[a]
AZD0865 25 mg vs AZD0865 50 mg	0.158
AZD0865 25 mg vs AZD0865 75 mg	0.898
AZD0865 50 mg vs AZD0865 75 mg	0.238
AZD0865 25 mg vs esomeprazole 20 mg	0.785
AZD0865 50 mg vs esomeprazole 20 mg	0.288
AZD0865 75 mg vs esomeprazole 20 mg	0.920

[a] p-values from the log-rank test.

Furthermore, no difference could be seen between the 3 doses of AZD0865 nor in comparisons to esomeprazole 20 mg regarding control of any other of the GERD symptoms or variables studied. Details are presented in the full report.

Safety results

Overall, AZD0865 was well tolerated. No SAEs were considered to be causally related to the study medication. The most commonly reported AEs were headache and various gastrointestinal symptoms with a similar frequency in all treatment groups. Reversible increases of transaminases more than 3 times the upper limit of normal (3 x ULN) were observed in some patients treated with AZD0865.

Table S3 Number (%) of patients who had an adverse event in any category, Safety Population

Category of adverse events[a]	AZD0865 25 mg (n= 363)	AZD0865 50 mg (n= 359)	AZD0865 75 mg (n= 362)	Esomeprazole 20 mg (n= 375)
Any adverse events	117 (32.2)	118 (32.9)	121 (33.4)	104 (27.7)
Any serious AEs	2 (0.6)	3 (0.8)	4 (1.1)	0
Serious AEs leading to death	0	0	0	0
Serious AEs not leading to death	2 (0.6)	3 (0.8)	4 (1.1)	0
Discontinuation of study treatment due to AEs	13 (3.6)	10 (2.8)	18 (5.0)	6 (1.6)
Other significant AEs	0	0	0	0
Severe AEs	13 (3.6)	14 (3.9)	22 (6.1)	11 (2.9)

[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 with maximal values>ULN during treatment, Safety Population

Lab variable		AZD0865 25mg n (%)	AZD0865 50mg n (%)	AZD0865 75mg n (%)	Esomeprazole 20mg n (%)
ALT	>ULN	62 (17.9)	70 (20.9)	66 (19.3)	77 (21.4)
	>2 x ULN	6 (1.7)	14 (4.2)	15 (4.4)	12 (3.3)
	>3 x ULN	2 (0.6)	7 (2.1)	12 (3.5)	1 (0.3)

Lab variable		AZD0865 25mg n (%)	AZD0865 50mg n (%)	AZD0865 75mg n (%)	Esomeprazole 20mg n (%)
	>5 x ULN	1 (0.3)	4 (1.2)	6 (1.8)	0 (0)
AST	>ULN	24 (6.9)	36 (10.7)	34 (9.9)	38 (10.6)
	>3 x ULN	0 (0)	4 (1.2)	5 (1.5)	0 (0)
ALP	>ULN	42 (12.1)	39 (11.6)	38 (11.1)	36 (10.0)
	>3 x ULN	0 (0)	1 (0.3)	2 (0.6)	0 (0)
Bilirubin, tot	>ULN	8 (2.3)	16 (4.8)	13 (3.8)	15 (4.2)
	>1.5 x ULN	1 (0.3)	5 (1.5)	3 (0.9)	2 (0.6)
	>2 x ULN	0 (0)	3 (0.9)	1 (0.3)	0 (0)

ULN upper limit of normal