AstraZeneca

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A randomised, double-blind, multicentre dose-finding Phase IIb study for up to 8 weeks' treatment with AZD0865 25, 50, 75 mg and esomeprazole 40 mg, given orally once daily for the healing of reflux esophagitis (erosive esophagitis) in adult patients with GERD with reflux (erosive) esophagitis according to the LA classification.

Study dates

First patient enrolled 13 May 2004

Last patient completed 18 March 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 healing of reflux esophagitis[1] according to Los Angeles (LA) classification at 4 weeks.

The secondary objectives were:

- To compare the efficacy of AZD0865 25, 50, 75 mg and esomeprazole 40 mg, with respect to healing of reflux esophagitis according to LA classification at 2, 4 and 8 weeks.
- To compare the efficacy of AZD0865 25, 50, 75 mg and esomeprazole 40 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 movement of materials upwards from the stomach. Various symptom variables were derived from these patient reported symptoms of which "the time to sustained absence of the individual symptom, defined as the time to the first of 7 consecutive days free of that symptom" regarding heartburn was considered the most informative.
- 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 40 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 pharmacokinetic population 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 2-8 weeks duration.

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

Target patient population and sample size

Male and female patients, 18 to 70 years with GERD with reflux esophagitis, ie, with 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 Mantel Haenzsel-Cochran test. Confidence intervals for the proportion of healed patients were estimated on the basis of normal approximations. The analysis of the secondary endpoints includes 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 summarized descriptively.

Patient population

The study population is considered to be adequately representative of the target population, ie, patients with reflux esophagitis and symptoms of GERD.

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 40 mg
Population					
n randomised (n planned)		389 (350)	380 (350)	375 (350)	377 (350)
Demographic characteristics					
Sex n (%)	Male	233 (60.4)	245 (65.0)	236 (62.9)	243 (64.6)
	Female	153 (39.6)	132 (35.0)	139 (37.1)	133 (35.4)
Age (years)	Mean (SD)	47.3 (12.1)	47.4 (12.2)	45.8 (13.1)	46.5 (13.2)
	Range	19 - 70	18 - 70	18 - 70	19 - 72
Race n (%)	Caucasian	342 (88.6)	340 (90.2)	326 (86.9)	328 (87.2)
	Black	11 (2.9)	11 (2.9)	16 (4.8)	12 (3.2)
	Oriental	1 (0.3)	2 (0.5)	3 (0.8)	1 (0.3)
	Other	32 (8.3)	24 (6.4)	30 (8.0)	35 (9.3)
Baseline characteristics					
Helicobacter pylori, positive n (%)		55 (14.3)	57 (15.1)	42 (11.2)	54 (14.4)
LA grade n (%)	A	132 (34.2)	127 (33.7)	144 (38.4)	131 (34.8)

		AZD0865 25 mg		AZD0865 50 mg		AZD0865 75 mg		Esomeprazole 40 mg	
	B	166	(43.0)	153	(40.6)	145	(38.7)	156	(41.5)
	C	69	(17.9)	73	(19.4)	65	(17.3)	73	(19.4)
	D	19	(4.9)	24	(6.4)	21	(5.6)	16	(4.3)
Intensity of symptom: A burning feeling behind your breastbone, n (%)									
	Mild	0	(0)	2	(0.5)	1	(0.3)	1	(0.3)
	Moderate	192	(49.7)	175	(46.4)	172	(45.9)	165	(43.9)
	Severe	188	(48.7)	193	(51.2)	192	(51.2)	207	(55.1)
	Missing	6	(1.6)	7	(1.9)	10	(2.7)	3	(0.8)
Disposition									
n of patients who	completed	365		344		345		352	
	discontinued	24		36		30		25	
n analysed for safety[a]		386		377		375		376	
n analysed for efficacy (ITT)		386		377		375		376	
n analysed for efficacy (PP)		289		282		279		289	

[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 healing of reflux esophagitis was approximately 80% (ITT) at 4 weeks for all doses of AZD0865.

Table S2 Healing rate at 4 weeks, ITT population

		Healing rate	95% confidence interval[a]	
Treatment arm	**n**	**%**	**Lower**	**Upper**
AZD0865 25 mg	386	76.9	72.4	81.1
AZD0865 50 mg	377	78.2	73.7	82.3
AZD0865 75 mg	375	81.1	76.7	84.9

[a] Confidence intervals are based on the normal approximation.

No differences could be seen, at any time-point studied (at 2, 4 or 8 weeks), between the 3 doses of AZD0865 (ITT). Neither could any consistant difference be observed for the 3 doses of AZD0865 in comparisons with esomeprazole 40 mg.

Table S3 Healing rate week 2, 4 and 8, ITT Population

Week	Treatment arm	n	Healing rate %	95% confidence interval[a] Lower	Upper	p-value[b]
2	AZD0865 25 mg	197	62.9	55.8	69.7	0.260
	AZD0865 50 mg	191	58.6	51.3	65.7	0.041
	AZD0865 75 mg	187	67.4	60.2	74.0	0.806
	Esomeprazole 40 mg	192	69.3	62.2	75.7	
4	AZD0865 25 mg	386	76.9	72.4	81.1	0.089
	AZD0865 50 mg	377	78.2	73.7	82.3	0.270
	AZD0865 75 mg	375	81.1	76.7	84.9	0.827
	Esomeprazole 40 mg	376	81.9	77.6	85.7	
8	AZD0865 25 mg	189	84.1	78.1	89.0	0.405
	AZD0865 50 mg	186	85.5	79.6	90.2	0.574
	AZD0865 75 mg	188	83.5	77.4	88.5	0.288
	Esomeprazole 40 mg	184	87.0	81.2	91.5	

[a] Confidence intervals are based on the normal approximation.

[b] p-values from the Cochran-Mantel-Haenszel test stratified by baseline LA grade comparing each dose of AZD0865 to esomeprazole 40 mg.

Regarding control of the cardinal symptom of GERD, ie, heartburn defined as “a burning feeling behind the breastbone”, no difference could be seen between the 3 doses of AZD0865 nor in comparisons to esomeprazole 40 mg. Furthermore, no differences were seen in any other of the GERD symptoms or variables studied. Details are presented in the full report.

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

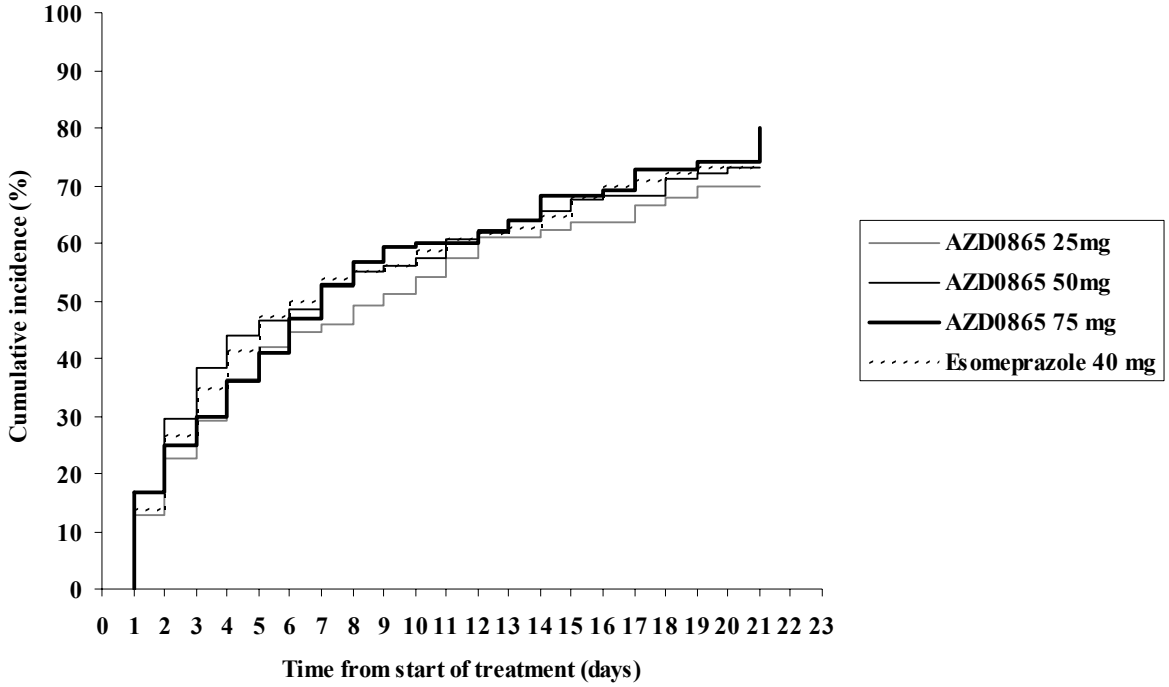

Table S4 Pairwise comparisons of treatments with respect to the cumulative incidence of sustained absence of a burning feeling behind the breastbone (day and night), ITT Population

Treatment comparison	p-value[a]
AZD0865 25 mg vs AZD0865 50 mg	0.143
AZD0865 25 mg vs AZD0865 75 mg	0.295
AZD0865 50 mg vs AZD0865 75 mg	0.766
AZD0865 25 mg vs esomeprazole 40 mg	0.194
AZD0865 50 mg vs esomeprazole 40 mg	0.847
AZD0865 75 mg vs esomeprazole 40 mg	0.881

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

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 S5 Number (%) of patients who had an adverse event in any category, Safety Population

Category of adverse events[a]	AZD0865 25 mg (n= 386)	AZD0865 50 mg (n= 377)	AZD0865 75 mg (n= 375)	Esomeprazole 40 mg (n= 376)
Any adverse events	123 (31.9)	130 (34.5)	121 (32.3)	113 (30.1)
Any serious AEs	2 (0.5)	1 (0.3)	1 (0.3)	0
Serious AEs leading to death	0	0	0	0
Serious AEs not leading to death	2 (0.5)	1 (0.3)	1 (0.3)	0
Discontinuation of study treatment due to AEs	10 (2.6)	12 (3.2)	9 (2.4)	8 (2.1)
Other significant AEs	0	0	0	0
Severe AEs	14 (3.6)	11 (2.9)	9 (2.4)	10 (2.7)

[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 S6 Number of patients with maximal values>ULN during treatment, Safety Population

Lab variable		AZD0865 25mg n (%)	AZD0865 50mg n (%)	AZD0865 75mg n (%)	Esomeprazole 40mg n (%)
ALT	>ULN	88 (23.2)	94 (26.0)	88 (24.6)	80 (21.9)
	>2 x ULN	12 (3.2)	11 (3.0)	14 (3.9)	4 (1.1)
	>3 x ULN	3 (0.8)	6 (1.7)	8 (2.2)	1 (0.3)
	>5 x ULN	2 (0.5)	4 (1.1)	5 (1.4)	0 (0)
AST	>ULN	33 (8.7)	36 (9.9)	33 (9.2)	25 (6.8)
	>3 x ULN	4 (1.1)	5 (1.4)	5 (1.4)	0 (0)
ALP	>ULN	48 (12.6)	40 (11.0)	36 (10.1)	38 (10.4)
	>3 x ULN	1 (0.3)	0 (0)	0 (0)	0 (0)
Bilirubin, tot	>ULN	14 (3.7)	15 (4.1)	10 (2.8)	10 (2.7)
	>1.5 x ULN	3 (0.8)	2 (0.6)	0 (0)	1 (0.3)
	>2 x ULN	1 (0.3)	0 (0)	0 (0)	0 (0)

ULN upper limit of normal