AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D9127C00002
Edition Number	1
Date	28 June 2011

A phase IIa, double-blind, randomized, 2-way cross-over study to evaluate the effect of a single dose of AZD1386 95 mg compared to placebo in a multimodal experimental pain model on esophageal sensitivity in GERD patients with a partial response to PPI treatment

Study dates: First subject enrolled: 4 November 2009
Last subject last visit: 12 January 2011

Phase of development: Therapeutic exploratory (IIa)

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

Study centre(s)

This study was performed in 2 study centres: one in Denmark and one in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare a single dose of AZD1386 to placebo on esophageal sensitivity to thermal stimuli 1.5 hours post dose in GERD patients who are partial responders to PPI	Time (sec) to VAS 7 during thermal stimulation (primary variable)	Efficacy
Secondary	**Secondary**	
To compare a single dose of AZD1386 to placebo on esophageal sensitivity to thermal stimuli 0.5 and 2.5 hours post dose in GERD patients who are partial responders to PPI	As described for the primary variable	Efficacy
To compare a single dose of AZD1386 to placebo on esophageal sensitivity to mechanical stimuli 0.5, 1.5 and 2.5 hours post dose in GERD patients who are partial responders to PPI	Bag volume (ml) at VAS 7 during mechanical stimulation	Efficacy
To compare a single dose of AZD1386 to placebo on esophageal sensitivity to electrical stimuli 0.5, 1.5 and 2.5 hours post dose in GERD patients who are partial responders to PPI	Current (mA) at VAS 7 during electrical stimulation	Efficacy
To assess the safety and tolerability of a single dose of AZD1386	Adverse events Laboratory variables: haematology, clinical chemistry, urinalysis Physical examination 12 lead ECG Vital signs: supine blood pressure and pulse Body temperature	Safety
To assess the pharmacokinetic properties of AZD1386	AUC_t, C_{max}, t_{max}	Pharmaco kinetic
To assess somatic pain by thermal and pressure stimuli on the arm as control experiments to esophageal (visceral) pain experiments	Temperature (°C) at VAS 7 during thermal stimulation Pressure (kPa) at VAS 7 during pressure stimulation	Efficacy

Objectives	Outcome variables	Type
To collect and store DNA for future exploratory research into genes that may influence response i.e. PK-profile, safety, tolerability and efficacy of AZD1386 treatment	Yet to be defined[a]	Pharmaco genetic

AUC_t Area under the plasma concentration versus time curve from time zero to the last quantifiable concentration, calculated by the log-linear trapezoidal method; C_{max} The observed maximum plasma concentration; GERD Gastroesophageal Reflux Disease; t_{max} Time to reach C_{max}; VAS Visual analogue scale (used for pain scoring); VAS 7 The stimulus intensity at which the patient reported moderate pain (corresponding to 7 on the VAS scale). Only the main outcome variable for each objective is presented; results of other variables are presented in the Clinical Study Report.

[a] In the case that pharmacogenetic analyses are performed, these will be presented in a separate study report.

Study design

This study had a double blind, two-way cross-over design comparing the effect of AZD1386 versus placebo on esophageal sensitivity in male and female patients with Gastroesophageal Reflux Disease (GERD) who were partial responders to proton pump inhibitors (PPIs).

Target subject population and sample size

Only patients with a history of GERD symptoms for 6 months (did not need to be consecutive) despite PPI treatment were to be included in the study. In addition, patients were to have been on optimized, unchanged PPI treatment with doses within the approved label for any GERD indication during the last 4 weeks prior to the pre-entry visit.

The initial target was to randomize 27 patients in order to get 20 evaluable patients. However, patient recruitment was slower than expected. Thus, the target number of evaluable patients was changed from 20 to 12.

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

AZD1386 oral solution 2.0 mg/mL (Batch number 09-000992AZ); placebo oral solution (Batch number 09-001559AZ; Batch number 09-001070AZ).

Duration of treatment

The patients received a single dose of AZD1386 95 mg or placebo in a 2-way crossover design. The two treatment periods were separated by ≥ 14 days. The follow-up visit occurred ≥7 days after the second treatment period.

Statistical methods

The statistical analysis was performed by Statistics and Informatics, AstraZeneca R&D Mölndal, using SAS version 8.2. A Statistical Analysis Plan was prepared before unblinding the data.

Esophageal sensitivity was defined as the pain tolerance threshold for mechanical, thermal and electrical esophageal stimuli, respectively. The pain tolerance threshold was defined as the level of stimulation on the Visual Analogue Scale (VAS) equal to 7 (ie, when the patient reported moderate pain).

Treatment effect differences between AZD1386 and placebo were to be estimated as either arithmetic mean differences or geometric mean ratios depending on whether the response variable was log-transformed prior to analysis or not. Based on the assumption of normality, data was analysed using a mixed linear model, with the fixed factors of centre, treatment, period and sequence, a random factor of patient nested within sequence and centre and an error term for observation within patients. For response variables where a pre-dose value was measured, the value was included in the model as a continuous covariate. 95% Confidence intervals for the true mean differences were calculated based on the percentiles from Student's t-distributions. All confidence intervals are presented unadjusted for multiple comparisons.

Subject population

Thirty patients were enrolled in the study (18 in Sweden and 12 in Denmark) and 14 patients were randomised (10 in Sweden and 4 in Denmark). One patient discontinued investigational product due to a Serious Adverse Event (SAE) but this patient did not receive AZD1386 at any time during the study. Another patient completed the study, but was incorrectly enrolled and was therefore excluded from the Per-Protocol (PP) analyses.

The patient population adequately represented the target population for the study. The patients were white, predominantly female (9 females versus 5 males) and aged between 21 and 69 years. All patients had persisting GERD symptoms, despite PPI treatment, as measured by the Reflux Disease Questionnaire (RDQ-RI) at the screening visit.

Summary of efficacy results

Esophageal sensitivity to thermal, mechanical or electrical stimuli was not significantly affected by AZD1386 95 mg compared to placebo in this study of GERD patients who were partial responders to PPI treatment. The analysis of the primary variable – time to VAS 7 during thermal stimulation of the esophagus – is shown in Table S2.

AZD1386 95 mg statistically significantly increased tolerance to somatic pain induced by thermal stimulation on the arm (positive control) compared to placebo. No treatment differences were seen when somatic pain was induced by pressure stimulation on the arm.

Table S2 Analysis of time to VAS7 (s) during thermal stimulation (PP analysis set)

Time after dose	Statistic	AZD1386 95mg (N=12)	Placebo (N=13)
00:30	Geometric mean[a]	86	87.8
	AZD1386/Placebo, geometric mean ratio (95% CI)	0.98(0.79,1.21)	
	AZD1386 vs Placebo, two-sided p-value[b]	0.845	
	AZD1386 vs Placebo, one-sided p-value[c]	0.577	
01:30	Geometric mean[a]	84	86.9

Time after dose	Statistic	AZD1386 95mg (N=12)	Placebo (N=13)
	AZD1386/Placebo, geometric mean ratio (95% CI)	0.97(0.78,1.2)	
	AZD1386 vs Placebo, two-sided p-value[b]	0.758	
	AZD1386 vs Placebo, one-sided p-value[c]	0.621	
02:30	Geometric mean[a]	85.5	77
	AZD1386/Placebo, geometric mean ratio (95% CI)	1.11(0.89,1.38)	
	AZD1386 vs Placebo, two-sided p-value[b]	0.336	
	AZD1386 vs Placebo, one-sided p-value[c]	0.168	

[a] Based on ANOVA of cross-over design
[b] Testing H0: AZD1386 = Placebo versus H1: AZD1386 ≠ Placebo
[c] Testing H0: AZD1386 ≤ Placebo versus H1: AZD1386 > Placebo

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Due to the low recruiting rate, only 13 patients were evaluated for efficacy instead of the original target of 20. Moreover, the variability in this study (SD=0.37) was greater than the predicted variability (SD=0.16) and also greater than the variability seen in the previous study with healthy volunteers (SD=0.23).

Summary of pharmacokinetic results

The geometric mean and confidence intervals for pharmacokinetic variables are shown in Table S3.

Table S3 Geometric means and confidence interval for pharmacokinetic variables of AZD1386 95 mg, oral doses (PP analysis set)

Variable	Geometric mean	95% Confidence interval	
		lower	upper
AUC_t(nmol*hr/L)	5899	4735	7349
C_{max}(nmol/L)	2361	1859	3000
T_{max}(hr)	1	0.5	2.5

[a] For T_{max}, geometric mean=median and confidence interval=range

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Summary of safety results

The safety analysis set consists of all randomised patients (n=14). Of these, 13 received a single oral dose of AZD1386 95 mg and 14 received placebo (2-way cross-over design).

No deaths were reported during this study. There was 1 SAE during the study and this SAE also caused the patient to discontinue treatment (DAE). This patient did not receive AZD1386 at any time during the study. No other DAEs were reported during the study.

Eleven patients had adverse events (AEs) during the AZD1386 treatment period and 2 patients had AEs during the placebo treatment period. The most commonly reported AEs following treatment with AZD1386 were feeling cold (7 patients), increased body temperature (4 patients) and oral hypoaesthesia (3 patients).

AZD1386 significantly increased body temperature, pulse, and blood pressure on the day of treatment compared to placebo, but all vital signs were similar at the pre-entry and follow-up visits. No significant or clinically relevant treatment-related differences were seen for laboratory safety variables, the QTcF interval or physical findings in this study.