AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D9127C00001
Edition Number	1
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A phase I, two centre, double-blind, randomized, cross-over study to evaluate AZD1386 in single doses of 30 mg and 95 mg compared to placebo in a multimodal experimental pain model on esophageal sensitivity and development of sensitization in healthy male volunteers

Study dates: First subject enrolled: 11 June 2008
Last subject last visit: 14 July 2009

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

The study was conducted at two centers, one in Denmark and one in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective of the study was to test the primary H_0 hypothesis: AZD1386 equals placebo in decreasing esophageal sensitivity* to thermal stimuli in a) the non-sensitized state, and b) in an acute chemical (acid)-sensitized* experimental state.	Time to VAS 7	efficacy
Secondary	**Secondary**	
To test the secondary H0 hypothesis: AZD1386 equals placebo in decreasing esophageal sensitivity* to mechanical and electrical stimuli in a) the non-sensitized state, and b) in an acute chemical (acid)-sensitized* experimental state	Volume at VAS 7 (mechanical stimulation) and intensity at VAS 1-7 (electrical stimulation)	efficacy
To show that AZD1386, in comparison with placebo, decrease esophageal sensitivity for chemical esophageal stimuli	Amount of acid at VAS 7	efficacy
To assess the safety and tolerability of single oral doses of AZD1386	Adverse events, laboratory variables, ECG, vital signs, body temperature	safety
To assess the pharmacokinetic properties after single oral doses of AZD1386 in male healthy volunteers	AUC, AUC_t, C_{max}, t_{max}, $t_{½}$, CL/F	pharmaco kinetic
To assess somatic pain by thermal and pressure stimuli on the arm as control experiments to esophageal (visceral) pain experiments	Pressure at VAS 7 and temperature at VAS 7	efficacy

* Definitions: Sensitivity is defined as the pain tolerance threshold (PTT) for mechanical, thermal, electrical and chemical esophageal stimuli, respectively. Sensitization is defined as a) the difference in PTT and/or b) the difference in referred pain area for mechanical, thermal and electrical esophageal stimuli, respectively, before compared to after esophageal infusion of acid.

Study design

This exploratory study had a double-blind, three-way cross-over design comparing both sensitivity and sensitization after a short acid infusion (0.1 M hydrochloric acid) in 22 healthy male volunteers before and after treatment with AZD1386 and placebo. Single doses of AZD1386, 30 mg and 95 mg, or placebo were administered as oral solution.

Target subject population and sample size

It was assessed that with 17 evaluable subjects, a two-sided 5% level paired t-test would have 90% power to detect a difference in time to PTT of 8 sec or a 7% increase in the geometric mean. Using 17 evaluable subjects, the probability that a 95% confidence interval of the ratio (R) will be no wider than 0.95*R to 1.05*R is 90%.

Assuming 70% of the enrolled subjects have a sensitisation potential and can be randomized into the study, at least 28 subjects should be enrolled in order to randomize 20 subjects and have 17 evaluable subjects.

All 22 healthy volunteers randomized in this study were included in the per-protocol analysis set and the safety analysis set.

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

Table S 2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD1386	Oral solution 2.5 mg/mL	AstraZeneca	H 2005-01-01	H 2005-01-01-03
PLACEBO	Oral solution Placebo	AstraZeneca	H 2006-02-01	H 2006-02-01-01

Duration of treatment

This study had a three-way cross-over design. In each study period, single doses of AZD1386, 30 mg and 95 mg, or placebo were administered as oral solution and there were at least 10 days wash-out between each of the three study periods.

Statistical methods

Comparisons of treatments (AZD1386 30 mg versus placebo and AZD1386 95 mg versus placebo) with respect to sensitivity and sensitization was primarily done by estimating contrasts of levels of treatment and measurement (I and II) and presented as mean differences with confidence intervals based on the normal distribution.

Based on the assumption of normality the analyses used a mixed linear model, with the fixed factors of centre, treatment, period and sequence, the pre dose measurement sensitivity as a continuous covariate, an interaction factor of treatment and measurement (I and II), a random factor of subject nested within sequence and centre and an error term for observation within subjects. Confidence intervals for the true mean differences were calculated based on the percentiles from Student's t-distribution.

Subject population

The subjects included in this study were all male healthy volunteers between 20 and 31 years of age. There was 1 Asian subject, the other 21 subjects were white. Prior to randomization the subjects were screened for sensitization potential, and only subjects that showed a difference in sensitivity between the measurements before and after acid infusion of more than 20% at the pain threshold in at least 2 of the 3 modalities were randomized into the study.

Summary of efficacy results

The analysis of the primary variable, time to VAS 7 after thermal stimulation showed that AZD1386 had an anti-nociceptive effect on heat induced pain. The time to VAS 7 was significantly longer for both the 30 mg and the 95 mg doses compared to placebo (one sided p-values <0.01 and 0.04 respectively). AZD1386 did not have an effect on sensitization, which is defined as the difference in sensitivity between before and after acid infusion. The degree of sensitization, expressed as the magnitude of the difference between before and after acid infusion, was not statistically different between AZD1386 treatment and placebo

AZD1386 did not display an anti-nociceptive effect on mechanically, electrically or chemically (acid) induced pain, ie, there were no statistically significant differences at VAS 7 after mechanical, electrical or chemical stimuli between AZD1386 treatment and placebo. Furthermore, AZD1386 did not have an effect on sensitization.

Measurement of somatic pain was included as a positive control to the esophageal (visceral) pain experiments. For the thermal stimuli, the somatic pain results correlated well with the esophageal pain results. For somatic mechanical stimuli, there was no effect of AZD1386, with the exception of a significant reduction at measurement I after the 30 mg dose.

Summary of pharmacokinetic results

The absorption of AZD1386 was considered to be fast. For the 30 mg dose median t_{max} was reached within 1 hour (0.76 hour) and for the 95 mg dose median t_{max} was reached at 1.13 hours.

The geometric mean apparent half-life ($t_{½}$) was estimated to be 5.6 hours for the 30 mg dose and 5.5 hours for the 95 mg dose.

Geometric mean CL/F (oral clearance calculated by dose/AUC) was 21.17 L/h after the 30 mg dose and 25.34 L/h after the 90 mg dose.

Geometric mean C_{max} after administration of AZD1386 was 763.5 nmol/L and 1832 nmol/L after single oral doses of 30 mg and 95 mg, respectively. The geometric mean AUC was 3815 and 10095 h*nmol/L for the 30 mg and 95 mg doses, respectively.

Summary of safety results

The number of subjects who experienced an adverse event (AE) during the active treatment periods was 17 at the 95 mg dose, 14 at the 30 mg dose and 5 at placebo. The AEs were mild

to moderate in intensity and the most commonly reported AE during treatment periods was "feeling cold". There were no SAEs after randomization (before randomization, one subject was found to be positive for HIV, which was regarded as an SAE).

There were no significant treatment related changes on laboratory safety variables. In particular, no clinically relevant AZD1386 related changes in liver enzymes were observed.

A transient decrease in QTcF was observed following administration of AZD1386. The QTcF shortening is in line with what has been observed in previous studies using single dose administration of AZD1386.

There was a significant increase in pulse and systolic blood pressure after 8 hours with the 95 mg dose. The increase in pulse is in line with what has been observed in previous studies using single dose administration of AZD1386.

An increase in body temperature was observed following administration of AZD1386 in line with what has been observed in previous studies using single dose administration of AZD1386.