AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D5090C00009
Edition Number	1
Date	8 September 2008

A double-blind, randomized, single-centre, placebo-controlled, crossover study to investigate the effects of a single oral dose of AZD1386 on intradermal capsaicin evoked pain symptoms and heat sensitivity in healthy volunteers

Study dates: First healthy volunteer enrolled: 30 January 2008
Last healthy volunteer completed: 26 May 2008

Phase of development: Therapeutic exploratory (II)

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

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Study centre(s)

The study was conducted at AstraZeneca's CPU Huddinge Hospital, Sweden. The first healthy volunteer enrolled on 30 January 2008, and the last healthy volunteer completed on 26 May 2008.

Publications

None at the time of writing this report.

Objectives

The primary objectives of the study were:

1. To evaluate the effects of orally administered AZD1386 on pain response evoked by intradermal capsaicin by assessment of pain intensity (continuous VAS ratings) at C_{max} and at time for maximal AZD1386 effect

2. To evaluate the effects of orally administered AZD1386 on heat pain threshold on non-sensitized skin at C_{max} and at time for maximal AZD1386 effect.

The secondary objectives of the study were:

1. To investigate the effects of AZD1386 on flare area/perfusion evoked by intradermal capsaicin

2. To investigate the effects of AZD1386 on warmth detection threshold on non-sensitized skin

3. To investigate the time-effect relationship of AZD1386 on intradermal capsaicin pain challenge by assessment of pain intensity and flare and on heat pain variables

4. To investigate brush allodynia area, thermal sensitivity and skin perfusion in topically capsaicin treated skin

5. To investigate Pharmacokinetics of AZD1386

6. To investigate safety and tolerability of AZD1386 by assessment of AEs, vital signs, body temperature, ECG, and standard laboratory variables

7. To investigate the PK/PD of AZD1386.

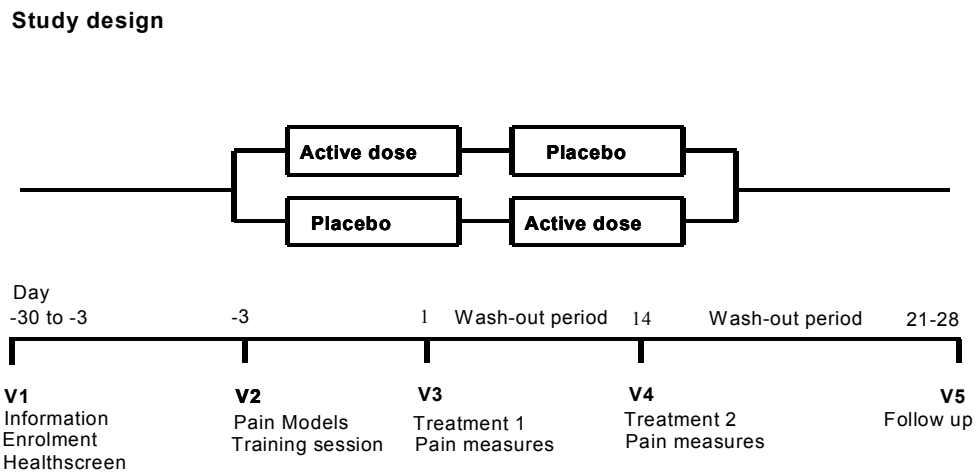
Optional for all participants:

Furthermore, a blood sample for genotyping will be collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect Pharmacodynamics and Pharmacokinetics, safety and tolerability related to AZD1386 treatment.

Study design

This was a Phase I, double-blind, randomized, single-centre, single-dose, placebo-controlled, crossover study conducted at AstraZenecas CPU, Huddinge Hospital, Sweden. Figure S 1. shows the design and sequence of treatment periods.

Figure S 1 Flow Chart of Study Design



Target healthy volunteer population and sample size

This study was to enrol 36 healthy male and non-fertile female subjects aged ≥20 to ≤45 years to evaluate the effects of a single oral dose of AZD1386 on intradermal and topical capsaicin-evoked pain symptoms.

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

95 mg AZD1386 oral solution, and placebo

Duration of treatment

Single dose

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary outcome variable

There were 4 primary outcome variables:

eVAS Pain $AUC_{0\text{-}5\ min}$ at 1h38min post-dose (t_{max}) and at 3h38min post dose, (decided at blind review to be the time for maximal AZD1386 effect), constituted 2 of the 4 primary variables.

Heat Pain Threshold (HPT) on non-sensitized skin at 1h30min post-dose (t_{max}) and at 3h30min post-dose, constituted the other 2 primary variables.

Secondary outcome variables

Pharmacodynamics: ·Intensity of pain (eVAS Maximum Pain) evoked by intradermal injection of capsaicin; warmth detection threshold (WDT) and HPT on skin sensitised with topical capsaicin; WDT on non-sensitized skin; Mechanical allodynia on skin sensitized with topical capsaicin; Erythema/Flare on skin sensitized with topical capsaicin; Erythema/Flare on skin sensitized by intradermal injection of capsaicin

Pharmacokinetics: Maximum plasma (peak) drug concentration (C_{max}); Time to reach C_{max} following drug administration (t_{max}); Area under the plasma concentration-time curve from time zero to infinity (AUC); Terminal half-life ($t_{1/2\lambda z}$), calculated as $\ln(2)/\lambda z$ is the terminal slope of the regression of ln concentration versus time; Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}); The oral plasma clearance (CL/F), calculated as dose/AUC

Criteria for evaluation - safety (main variables)

Adverse events, vital signs, oral body temperature, ECG and standard laboratory variables.

Statistical methods

Linear mixed effects model with repeated statement were utilized in the analysis of non-transformed values of HPT. The model includes treatment, sequence and period as fixed factors, subject (within sequence) as a random factor and time as a repeated factor. Contrast option was used for comparison of AZD1386 versus placebo at t_{max} and at time for maximal effect. Least square means of treatment difference and corresponding 90% confidence intervals have been calculated.

Blind review of data revealed that eVAS AUC values of measurements were not normally distributed (Gaussian). Therefore it was decided to use a non-parametric method for analysis of this variable. Koch's adaptation of the Wilcoxon-mann-Whitney rank sum test was used. The Hodges-Lehmann estimator and corresponding 90% confidence intervals of the treatment difference have been calculated.

Linear mixed effects model with repeated statement were utilized in the analysis of non-transformed values of WDT, temperature and $\log_e$-transformed values of flare variables and mechanical allodynia. For transformed variables results were exponentially back-transformed to provide the results for the ratios of interest (AZD1386/placebo).

For eVAS Pain Maximum variable the same statistical analysis procedure as described above for eVAS AUC was used.

All statistical tests were at the 10% significance level (ie, α=0.10 two-sided). The primary analyses were adjusted for multiplicity (using Hommel's method) and report adjusted p-values.

The statistical analysis of AEs, vital signs, oral body temperature, ECG and standard laboratory variables is primarily descriptive.

Subject population

The subject population and disposition are summarised in Table S 1.

Table S 1 Subject population and disposition (D5090C00009)

Demographic or baseline characteristic		Study population
		AZD1386/Placebo
Population		
N of randomized		36 (100%)
Demographic characteristics		
Sex	Male	36 (100%)
Age (years)	Mean	27.7
	Range	20 - 45
BMI (kg/m^2)	Mean	23.5
	Range	18.5-29.0
Body weight (kg)	Mean	76.6
	Range	58.0-100.0
Race n(%)		
	White	35 (97.2%)
	Black	1 (2.8%)
Disposition		
N of subjects who	Completed	35 (97%)
	Discontinued	1 (3%)
N of subjects analysed for safety		36 (100%)
N of subjects analysed for PD		35 (97%)
N of subjects analysed for PK		36 (100%)

The 36 randomized subjects in the study comprised healthy male subjects with a mean age of 27.7 years (range 20 to 45 years). This subject population could be considered appropriate for this type of study using human pain models. Concomitant medications were used infrequently in the study and in all instances were used after agreement with the principal investigator. The intake of the concomitant medicine occurred after effect assessments and therefore did not influence results. One subject voluntarily withdrew from the study following treatment with AZD1386 and prior to receiving placebo. This subject was excluded from the PD analysis, as

a comparison with placebo could not be undertaken. However, as the subject had received study drug, he was included in the PK and safety analysis sets. The dropout was considered not to be a major protocol deviation. All subjects received the correct allocated investigational product.

Summary of efficacy results

AZD1386 at a single dose of 95 mg was not superior to placebo in decreasing intensity of pain evoked by intradermal injection of capsaicin, as assessed by eVAS $AUC_{0\text{-}5\ min}$ for the 2 timepoints chosen as primary variables (adjusted p-values p=0.063 and p=0.229 for 1h38min and 3h38min, respectively). AZD1386 was superior to placebo in increasing heat pain threshold on non-sensitized skin at 1h30min and 3h30min (adjusted p-values p<0.001), the 2 timepoints chosen as primary variables. Results from the primary efficacy analyses (eVAS $AUC_{0\text{-}5min}$, HPT) are summarized in Table S 2.

Table S 2 Summary of results of primary efficacy analyses comparing AZD1386 versus placebo (PD analysis set) (D5090C00009)

		AZD1386	Placebo				
Variable	**Type of estimate**	**n**	**n**	**Trt group comparison**	**90% CI**	**Unadj p-value**	**Adj p-value**
eVAS AUC at 01:38	HL est. of difference	34	35	-606.3	-1280.1 , -48.58	0.031	0.063
eVAS AUC at 03:38	HL est. of difference	35	34	-407.5	-1090.7 , 334.71	0.229	0.229
HPT at 01:30	LS means of difference	35	35	4.41	3.90 , 4.93	<.001	<.001
HPT at 03:30	LS means of difference	35	35	3.57	3.05 , 4.08	<.001	<.001

The clinical hypothesis is that AZD1386 leads to lower level of pain and/or a higher HPT then placebo
Koch's adaptation of the Wilcoxon-Mann-Whitney rank sum tests was used to generate the confidence intervals and p-values for eVAS AUC.
HL est. are Hodge-Lehmann estimates of differences AZD1386-placebo
Mixed linear model with repeated statement was used to generate the confidence intervals and 1-sided p-values for HPT.
LS means are least square means of differences AZD1386-placebo
Adj p-values are p-values adjusted using the Hommel's multiple comparison procedure.
Adjusted p-values are one-sided.
eVAS AUC (Area Under Curve) values are given in mm*sec and HPT (Heat Pain Threshold) values are given in °C.
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Summary of pharmacodynamic results

AZD1386 was superior to placebo in decreasing the intensity of pain at all timepoints (p<0.001 at each timepoint), as assessed by maximum eVAS rating after intradermal injection of capsaicin. The largest treatment difference was observed at 1h38min. Following AZD1386 treatment, the decrease at this time point in maximum eVAS was –26.5 mm (Hodge-Lehmann estimate) compared to placebo treatment.

AZD1386 increased HPT and WDT in comparison to placebo on skin sensitized with topical capsaicin, and on non-sensitized skin, at all timepoints.

A decreased area of mechanical allodynia on skin sensitized by topical capsaicin was seen in subjects treated with AZD1386 compared with placebo-treated subjects at 3h18min, but not at 5h18min.

AZD1386 was superior to placebo in reducing flare area, mean perfusion and mean flare perfusion on skin sensitized with topical capsaicin. AZD1386 was superior to placebo in reducing mean perfusion (intensity) on skin sensitized with intradermal capsaicin at 1h18min, 1h38min and 2h38min, but not at later timepoints. AZD1386 was also superior to placebo in reducing mean flare perfusion at 1h18min and 1h38min, and superior to placebo in reducing flare area at the 3h38min timepoint only.

Summary of pharmacokinetic results

Following administration of AZD1386, 95 mg as an oral solution at fasting conditions, median t_{max} was found at 1 h (range 0.5-4 h). Geometric mean C_{max} was 1771 nmol/L (CV 31%) and geometric mean AUC_{0-8h} was 7,346 nmol*h/L (CV 34%). There was an approximately 3.5-fold difference between the highest and lowest C_{max} and AUC_{0-8h}, respectively.

Summary of pharmacokinetic/pharmacodynamic relationships

A relationship between plasma concentrations and effects was observed in the sense that in general the maximum effects were observed at or close to the time of maximum concentrations. The response also seemed to be larger with higher plasma concentrations, although there was large variability in the response.

Summary of pharmacogenetic results

Not reported in this CSR.

Summary of safety results

There were no major safety or tolerability concerns identified with a single 95 mg dose of AZD1386. Feeling cold and headache were the most commonly observed AEs. All AEs were either mild or moderate in intensity. There were no deaths, SAEs or discontinuations due to adverse effects. There were no clinically relevant effects of AZD1386 treatment on haematology, clinical chemistry or vital signs.

AZD1386 treatment resulted in a slight increase in mean oral body temperature compared with placebo treatment (≤0.33 ºC at all timepoints). The highest individual oral body temperature recorded was 38.1 °C, recorded in 1 subject at a single timepoint. The increase in oral body temperature was not considered clinically relevant on either the group or individual level.