AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D5090C00019
Edition Number	1
Date	17 December 2009

A Phase II Randomised, Double-blind, Parallel Group, 4-week treatment, Adaptive Dose Finding, Multi-centre study evaluating the Efficacy, Safety, Tolerability and Pharmacokinetics of up to three different oral doses of AZD1386 and Placebo in patients with Osteoarthritis of the knee

Study dates: First patient enrolled: 25 March 2009
Last subject last visit: 30 July 2009

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

This study was conducted in 7 countries at 41 sites in Europe, Japan and North America.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives[a]	Outcome variables	Type
Primary	**Primary**	
The primary objectives are to evaluate the relationship between dose and analgesic efficacy of AZD1386 and evaluate the analgesic efficacy of AZD1386 in patients with osteoarthritis of the knee.	The dependent variables was mean of change from baseline to Week 2 (V4) and Week 4 (V5) in WOMAC pain subscale, 48 hours recall.	Efficacy
Secondary	**Secondary**	
To evaluate the analgesic efficacy of AZD1386 during the night and day, in patients with osteoarthritis of the knee.	NRS pain intensity, 12 hours recall, in the morning and evening.	Efficacy
To evaluate the efficacy regarding function and stiffness and relationship between dose and efficacy of AZD1386 in patients with osteoarthritis of the knee.	WOMAC function subscale, WOMAC stiffness subscale and WOMAC total score, 48 hours recall.	Efficacy
To evaluate the percentage responders for AZD1386.	Responder defined according to OARSI/OMERACT.	Efficacy
To investigate the safety and tolerability of AZD1386.	Physical examination, laboratory values, vital signs (blood pressure, pulse rate and body temperature) and ECG including QTcF. AEs including frequency and severity AEs leading to withdrawals.	Safety
To evaluate the difference in use of rescue medication (paracetamol/acetaminophen) between AZD1386 and placebo.	Amount of rescue medication and percentage of patients taken rescue medication.	Efficacy

[a] The results from the exploratory objectives in this study are described in the clinical study report.

AE: Adverse event, WOMAC: Western Ontario and McMaster Osteoarthritis Index, QTcF: QT interval corrected for heart rate using the Fredericia formula.

Study design

This was a 6 week multi-centre Proof of Concept (PoC) study with a double-blind, placebo-controlled, randomised, adaptive dose-finding design. It evaluated the efficacy, safety, tolerability and PK of different oral doses of AZD1386 and placebo in patients with osteoarthritis of the knee.

The study design included two stages, with an interim analysis for futility in between. A Data Monitoring Committee (DMC) performed the Stage 1 interim analysis. Based on the interim data, the DMC decided that the study was to be stopped after Stage 1, since the criteria for continuing into stage 2 were not met.

Target subject population and sample size

This study included non-hospitalised patients, both male and female**, ≥**40 - <80 years with primary osteoarthritis of the knee, diagnosed according to American College of Rheumatology (ACR) guidelines and verified by X-ray (corresponding to at least grade 2 according to Kellgren). The ACR class had to be functional class I–III.

Patients with past or ongoing intolerability to NSAID´s/COX-2`s or paracetamol/ acetaminophen or patients with insufficient pain relief from these treatments were included in the study. The WOMAC pain on walking had to be ≥40 mm and ≤90 mm on a Visual Analogue Scale (VAS) at both the enrolment and randomisation visits.

A treatment effect of 8 units on WOMAC pain for the highest dose compared to placebo and a standard deviation of 22 was assumed. A sample size of 110 evaluable patients per treatment group was anticipated to yield a power of 90% for the primary test at a significance level of 10% (one-sided). A total of 241 patients were randomised into the study and 231 patients were considered evaluable for analysis of efficacy. The primary analysis included 99 patients in the AZD1386 90 mg dose group and 90 patients in the placebo group.

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

The dose (30 mg AZD1386, 90 mg AZD1386 or placebo) was taken twice daily, morning and evening, approximately 12 hours apart, and swallowed whole together with water, with or without food.

For the 30 mg dose, 3 capsules of 10 mg each was given (Batch 08-002012AZ). For the 90 mg dose, 3 capsules of 30 mg each was given (Batch 08-002010AZ) and for placebo, 3 matching capsules were given (Batch 08-002337AZ).

Paracetamol/acetaminophen was allowed as rescue medication. The maximum dose of paracetamol/acetaminophen was 4 gram/day in all countries except Japan, where 1.5 gram/day was allowed. The rescue medication was sourced and labelled locally in each country by the distribution sites, or sourced and labelled by IPS Sweden.

Duration of treatment

The treatment period was 4 weeks.

Statistical methods

The analyses of efficacy were based on a full modified Intention to Treat (ITT) analysis set, including all patients with both a baseline and at least one post-baseline value for the primary variable (WOMAC Pain). The analyses of safety and PK data were based on the safety analysis set, including all patients who received at least 1 dose of randomised IP and for whom post-dose data were available.

Statistical methods for primary efficacy

A linear mixed model was used to compare the primary variable in the different AZD1386 dose groups with placebo. The model included the WOMAC pain subscale baseline and treatment group as fixed effects and site as a random effect. Least square means (LSmeans) for each treatment as well as for each of the differences (AZD1386-placebo) was obtained from this model. The corresponding 95% two-sided confidence interval for each of the differences was also constructed. The one-sided p-value for the comparison between both AZD1386 dose groups and placebo was compared with $\alpha = 2.5\%$. No correction of multiplicity was performed on the p-values.

If both the WOMAC pain score at week 2 and week 4 were missing, the score at week 1 was used instead (last observation carried forward approach).

Statistical methods for secondary efficacy

The mean of the change from baseline week 2 and week 4 in WOMAC function/stiffness/total score was analysed in the same way as for the primary outcome variable. The p-values for these tests were not corrected for multiplicity.

For NRS, the change from baseline in NRS Pain intensity at Week 4 was analysed using a mixed model with repeated measures. The model included day-treatment group-interaction as fixed effects and patient, site as random effects. As part of a post-hoc sensitivity analysis the NRS pain intensity at Week 4 change from baseline was analysed with the same linear mixed model used for the primary analysis. For both NRS analyses, day and night scores were analysed separately.

The percentage of responders was analysed using the Cochran-Mantel-Henzel test, comparing the different dose groups with placebo. The mean daily intake of rescue medication was analysed using a mixed model comparing the different dose groups with placebo.

Subject population

In total, 241 of 327 enrolled patients were randomised into the study. One of these never received any study drug. As many as 87% of the patients completed the study . The most common reason for discontinuing the study was an AE (18 patients)

Overall, the included patient population appeared to be in accordance with the inclusion criteria, i.e. either with intolerability to nsNSAIDs/COX-2s or with unsatisfactory pain relief from nsNSAID/COX-2 or paracetamol/acetaminophen treatment.

The age, sex and BMI of the patients were representative for the OA population and well-balanced between the treatment groups. The mean age was 62 years, the mean BMI 31 and around 70% of the patients were women. The mean WOMAC pain on walking was similar between the treatment groups at baseline (63 to 65 mm) and within the set inclusion criteria (i.e. between ≤ 40 mm and ≥ 90 mm).

Summary of efficacy results

AZD1386 was not effective in reducing pain compared to placebo at any of the doses tested, as assessed by the primary variable (see Table S2).

Table S2 Comparison of the mean of week 2 and week 4 change from baseline in WOMAC Pain (mm) for AZD1386 vs placebo (ITT analysis set)

		Mean of week 2 and week 4 change from baseline in WOMAC Pain (mm)		Difference from placebo		
Treatment	**n**	**LSmean estimate**	**95% CI**	**LSmean estimate[a]**	**95% CI**	**One-sided p-value**
Placebo	90	-17.54	(-21.55, -13.52)			.
AZD1386 30 mg	42	-20.05	(-25.75, -14.34)	-2.51	(-9.21, 4.19)	0.2302
AZD1386 90 mg	99	-19.05	(-22.89, -15.21)	-1.52	(-6.72, 3.69)	0.2834

A linear mixed model with baseline and treatment group as fixed effects, and centre as random effects was used, contrast estimations were used to generate the p-values.
a Differences less than 0 show WOMAC Pain subscale score is lower in AZD1386 treatment than in Placebo.
Source: T_womPain_mixed. SAS Generated: 17:13:09 04Nov2009 DB version prod: 8

The mean WOMAC pain decreased over time in all treatment groups and there were no significant differences between AZD1386 and placebo at any visit. The largest part of the improvement was observed during the first two weeks of treatment.

The results of the WOMAC function, WOMAC stiffness and WOMAC total scales were in line with the results of the primary analysis. AZD1386 did not improve patient physical functioning or decrease stiffness compared to placebo at any of the doses tested, as assessed by the change in mean WOMAC function and stiffness subscale scores to Week 2 and 4.

The NRS results were in accordance with the WOMAC data. AZD1386 was not effective in reducing mean pain intensity during the night or the day compared to placebo, as assessed by the change in mean NRS pain intensity to Week 4.

The percentage of responders was not higher for AZD1386 than for placebo, as assessed by OARSI/OMERACT criteria and there was no significant difference between AZD1386 and placebo in the mean daily intake of rescue medication.

Summary of pharmacokinetic results

The plasma sampling for analysis of AZD1386 was not optimised for calculating any PK parameters, and since the study was prematurely stopped, no formal PK analysis has been performed. The observed plasma concentrations of AZD1386 were in agreement with what was expected, based on results in previous studies. The highest observed plasma concentration was 7520 nmol/L.

Summary of safety results

There were three serious adverse events (SAEs) in this study. One occurred before randomisation, one occurred in the placebo group and one occurred in the 30 mg dose group. None of the SAEs were related to the IP, as judged by the investigators.

Overall, the incidence of adverse events and discontinuations due to adverse events were more common in the AZD1386 dose groups than in the placebo group. Eighteen, or 7.5% of the patients discontinued their treatment due to an AE, including 3 (6.8 %) of the patients in the 30 mg dose group, 12 (11.7%) of the patients in the 90 mg dose group and 3 (3.2%) of the patients in the placebo group. A majority of the adverse events were mild to moderate in intensity. The most common types of adverse events included altered sensations/sensory perceptions in the mouth and feelings of warmth and coldness. Burns of mild to moderate intensity were reported in eight patients on AZD1386. None of the burns were classified as an SAE and none of the affected patients discontinued due to these events.

Individual increases in hepatic enzymes were observed in 9 patients on 90 mg AZD1386 after 4 weeks of *bid* dosing. There were no increases in hepatic enzymes after 2 weeks of dosing. No assessments were made between the second and fourth week of treatment. Six patients in the 90 mg dose group had S-ALT increases to above 3 times the upper limit of normal (ULN). Five of these also had increases in other hepatic enzymes, including one patient with an increase in bilirubin accompanied by jaundice and pruritus, which reversed. Another 3 patients in the 90 mg dose group had increases in S-ALT close to 2 times the ULN, accompanied by a small increase in S-AST. Reversibility of the hepatic enzyme elevations has been confirmed in most of the patients.

None of the patients in the AZD1386 30 mg and placebo groups had increases in hepatic enzymes to above 3 times ULN. There were no other clinically important differences between the treatment groups in clinical chemistry or haematology variables.

There was no difference in mean body temperature between AZD1386 and placebo and no apparent differences between treatment groups in other vital signs. Furthermore, there were no clinically important differences in mean QTcF between AZD1386 and placebo and no apparent differences between treatment groups in other ECG variables