AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00016
Edition Number	1.0
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A Phase IIa, Double-Blind, Randomised, Parallel-Group, Multi-Centre Study to Evaluate the Analgesic Efficacy of 28 Days Oral Administration of AZD2066 with One-Dose Escalation Compared to Placebo in Peripheral Neuropathic Pain Patients with Mechanical Hypersensitivity

Study dates:

First subject enrolled: 03 August 2009
Last subject last visit: 08 November 2010
Date of early study termination: 05 October 2010 (safety reasons)

Phase of development:

Therapeutic exploratory (II)

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

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 evaluate the analgesic efficacy of 28 days of oral administration of AZD2066 compared to placebo in peripheral neuropathic pain patients with mechanical hypersensitivity.	The change in mean pain intensity from 5-day baseline (Day –5 to Day –1) to the last 5 days of treatment, measured twice daily with Numerical Rating Scale (NRS) (12-hour recall)	Efficacy
Secondary	**Secondary**	
To evaluate the response rate of patients to AZD2066 versus placebo	Responder rate, where responders are defined as patients with: − Pain intensity score reduction by ≥30% at Day 28 compared to baseline − Pain intensity score reduction by ≥50% at Day 28 compared to baseline − At least "much improved" on Patient Global Impression of Change (PGIC) at Day 28	Efficacy
To evaluate the effect of AZD2066 on different components of pain compared to placebo	The change from baseline in Brief Pain Inventory Short Form (BPI-SF) and Short Form McGill Pain Questionnaire (SF-MPQ)	Efficacy
To investigate the pharmacokinetics (PK) of AZD2066	AZD2066 plasma concentrations	PK
To evaluate the safety and tolerability of AZD2066	Adverse event (AE) frequency, and severity; withdrawals due to AE; laboratory safety; vital signs; 12-lead electrocardiogram (ECG)	Safety
Exploratory	**Exploratory**	
To explore the effect of AZD2066 versus placebo upon stimulus-evoked neuropathic pain (mechanical allodynia and/or punctate hyperalgesia)	Change in area of mechanical allodynia from Visit 3 (pre-dose) to each study visit Change in NRS score from before to after evoking punctate hyperalgesia with Von Frey hairs at each visit Change in NRS score from before to during evoking mechanical allodynia with a standardized brush at each visit	Efficacy

Objectives	Outcome variables	Type
To explore the relationship between drug concentrations in plasma and safety and efficacy variables	AZD2066 plasma concentrations, safety variables, efficacy variables.	Efficacy
To explore the effects of AZD2066 compared to placebo on the consumption of rescue medication	The average number of occasions rescue medication was used per day in study or the average dose of rescue medication per day and the frequency of patients using rescue medication	Efficacy
To describe the time course of rated pain after end of treatment with AZD2066 up to follow-up	The change of the mean pain intensity from the last 5 days on treatment to the last 3 days in the study (including Visit 8), measured twice daily with NRS (12-hour recall). The change in SF-MPQ and BPI-SF from Day 28 to follow-up.	Efficacy

Note: The results from the exploratory objectives are not included in the Clinical Study Report (CSR) synopsis but are presented in CSR D0475C00016.

Study design

This was a multi-centre, Phase IIa study with a double-blind, placebo-controlled, randomised, parallel group, 1 dose escalation design evaluating the efficacy and safety of 28 days of treatment with AZD2066 in patients with neuropathic pain associated with mechanical hypersensitivity (NP-MH).

Target subject population and sample size

Male or female patients aged 18 to 80, inclusive, with a clinically established diagnosis of neuropathic pain associated with mechanical allodynia and/or punctate hyperalgesia and a NRS pain intensity score of ≥4 to ≤9 at enrolment (7-day recall) and at randomisation (average of 5-day 12-hour recall).

The original plan was to randomise a sufficient number of patients (approximately 100) in order to reach 80 evaluable patients. However, based on AstraZeneca's decision, following a serious adverse event (SAE), the study was prematurely stopped with 87 patients randomised (68 evaluable patients).

With 40 patients treated with AZD2066 and 40 patients receiving placebo, there was 90% power for AZD2066 to be statistically significant better than placebo at a significance level at 10% (1-sided). The sample size was calculated to test the null hypothesis H0: no difference between AZD2066 and placebo with regards to the primary efficacy variable versus the alternative hypothesis H1: the true difference is 1.2. The standard deviation (SD) was assumed to be 2.1.

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

AZD2066: 12 mg Days 1 to 4 and 18 mg Days 5 to 28, administered orally once daily in the morning together with breakfast

Placebo: AZD2066 placebo capsule, administered orally, once daily in the morning together with breakfast

Rescue medication was provided by the investigators.

Batch numbers were as follows:

AZD2066 2 mg capsules: 08-001811AZ
AZD2066 8 mg capsules: 08-001815AZ
Placebo capsules: 08-001091AZ

Duration of treatment

The study comprised 3 phases: an enrolment phase of up to 35 days (including washout period and baseline period), a 28-day treatment phase, and a follow-up phase of 7 days (for men and women not of childbearing potential) or 28 days (for women of childbearing potential). Patients randomised to treatment with AZD2066 received AZD2066 12 mg from Days 1 to 4 and 18 mg from Days 5 to 28.

Statistical methods

All statistical tests were 1-sided with a significance level of 10%.

The primary outcome variable, the change in mean NRS score from the average of values measured between and including Day -5 to -1 (baseline) to the average of values measured at the last 5 days on treatment, were analysed using a mixed model analysis with mean NRS score at baseline as a covariate and including treatment as a fixed effect and centre as a random effect. The comparison of interest was the difference between AZD2066 and placebo.

Where appropriate, secondary efficacy analyses report nominal p-values to aid the interpretation of results. No adjustments for multiplicity were made for these secondary analyses.

Subject population

A total of 302 patients were enrolled in the study. Of these, 87 were randomised to AZD2066 (42 patients) and placebo (45 patients). Of the 87 patients randomised, 72.4% (63/87 patients) completed treatment and 27.6% (24/87 patients) discontinued treatment. The most common reason for discontinuing study treatment in the AZD2066 group was occurrence of an AE (9/42 patients, 21.4%), while the most common reason for discontinuing study treatment in the placebo group was subject decision (6/45 patients, 13.3%).

In general, with the exception of gender, demographic characteristics were similar between the AZD2066 and placebo groups. Overall, the mean age was 58.7 years (range 19 to 80 years). Most patients (90.8%) were White. Overall, 51.7% of patients were male and 48.3% were female; however, the percentage of male patients was lower and the percentage of female patients was higher in the AZD2066 group (42.9% male and 57.1% female) than in the

placebo group (60.0% male and 40.0% female). Baseline NRS pain intensity scores were similar in the AZD2066 and placebo groups.

Summary of efficacy results

- Patients treated with AZD2066 had a statistically significantly greater reduction in pain intensity than the placebo-treated patients after 28 days of treatment, as assessed by the change from baseline in NRS pain score.

- Patients treated with AZD2066 were statistically significantly more likely to have a response in terms of pain reduction than the placebo-treated patients after 28 days of treatment, as assessed by the secondary efficacy variables of a reduction in the NRS pain score of at least 30% or 50%.

- After 28 days of treatment, there was no statistically significant difference in the likelihood of patients having PGIC scores of "much improved" or "very much improved" between the AZD2066 and placebo groups, but the percentage of patients who were PGIC responders was numerically higher in the AZD2066 group.

- Patients treated with AZD2066 had a statistically significantly greater reduction in SF-MPQ Sensory Index scores than placebo treated patients at Day 28. However, there were no statistically significant differences between the AZD2066 and placebo groups in SF-MPQ Affective Index or SF-MPQ Pain Rating Index scores.

- Patients treated with AZD2066 had a statistically significantly greater reduction in BPI-SF Pain Severity scores than placebo treated patients at Day 28. However, there was no statistically significant difference between the AZD2066 and placebo groups in BPI-SF Pain Interference scores.

Summary of pharmacokinetic results

The PK of AZD2066 was adequately described using a 1-compartment model with first-order absorption. Oral clearance (CL/F) was found to be 59% higher in males than in females, with mean population CL/F estimates of 0.75 L/h (females) and 1.20 L/h (males). Based on all data, CV (%) in CL/F was 39%. By accounting for differences in CL/F between the genders the variability was decreased to 33%. Oral volume (V/F) was positively correlated to body weight. The mean population V/F was estimated to 55 L, which changed with 7.6 L for every 10 kg deviation from the median body weight. The between-patient variability in V/F was estimated to 27% (without covariates). In the final model, after inclusion of covariates no significant unexplained between-patient variability was present.

The mean estimated plasma concentration at steady state (range) was 2607 (1426-4162) nmol/L and 1643 (985-3225) nmol/L after QD administration of 18 mg AZD2066 to females and males, respectively.

Summary of safety results

- There were no deaths during the study.
- There was 1 SAE in a patient who received IP. Patient E1218006 in the AZD2066 treatment group experienced a severe psychotic episode 1 day after discontinuing IP. This event resulted in hospitalization and was considered an important medical event. Following this SAE, AstraZeneca terminated the study.
- The incidence of patients experiencing any AE was higher in the AZD2066 group (30 [71.4%] patients) than the placebo group (22 [50.0%] patients).
- Nine patients (21.4%) in the AZD2066 group experienced AEs leading to the discontinuation of IP compared with no patients in the placebo group. Four of these 9 patients experienced an AE in the Psychiatric Disorders System Organ Class (SOC) that led to discontinuation of IP.
- AEs most commonly occurred in the SOCs of Nervous System Disorders and Psychiatric Disorders. The incidence rate of AEs within these SOCs was higher in the AZD2066 group than in the placebo group.
- The most common AEs in the AZD2066 group (reported by ≥5% of patients in the AZD2066 group) were dizziness, headache, arthralgia, diarrhoea, insomnia, paraesthesia, and somnolence. The incidence of all of these AEs was higher in the AZD2066 group than in the placebo group.
- Most AEs were mild or moderate in intensity with 4 patients in the AZD2066 group and 1 patient in the placebo group reporting any severe AEs.
- There were no meaningful differences between AZD2066 and placebo in any of the laboratory parameters, vital signs, ECG variables, physical examination findings, weight, or body mass index.