AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00009
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 Compared with Placebo in Patients with Painful Diabetic Neuropathy

Study dates: First patient enrolled: 27 February 2009
Last patient last visit: 24 August 2009

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 with placebo in patients with painful diabetic neuropathy (PDN)	Change of mean pain intensity from 5-day baseline to the last 5 days of treatment, measured twice daily with Numerical Rating Scale (NRS) (12 hours recall)	Efficacy
Secondary	**Secondary**	
To evaluate the response rate of AZD2066 versus placebo	Daily NRS pain scores Responder rate, where responders were defined as patients with: -pain intensity score reduction by ≥30% (NRS) at Day 28 compared to baseline -pain intensity score reduction by ≥50% (NRS) at Day 28 compared to baseline -at least "much improved" on Patient Global Impression of Change (PGIC)	Efficacy
To evaluate the effect of AZD2066 on different components of pain compared with placebo	Change from baseline in Brief Pain Inventory Short Form (BPI-SF) Change from baseline in McGill Pain Questionnaire Short Form (MPQ-SF)	Efficacy
To investigate the pharmacokinetics (PK) in patients with PDN	AZD2066 plasma concentrations	PK
To evaluate the safety and tolerability of AZD2066	Adverse events (AEs), laboratory safety, vital signs and electrocardiogram (ECG)	Safety
Exploratory	**Exploratory**	
To explore the effects of AZD2066 compared with placebo on the consumption of rescue medication	The number of occasions rescue medication used	Efficacy
To explore the relationship between drug concentrations in plasma and safety and efficacy variables	AZD2066 plasma concentrations, safety variables, efficacy variables	Efficacy
To describe the time course of rated pain after end of treatment with AZD2066 up to follow-up	Change of mean pain intensity from the last 5 days on treatment to the last 3 days in the study (including the follow-up visit), measured twice daily with NRS (12 hours recall)	Efficacy

Note: The results from the exploratory objectives are not included in the Clinical Study Report (CSR) synopsis but are presented in CSR D0475C00009.

Study design

This was a multi-center Proof of Principle study with a double-blind, placebo-controlled, randomized, parallel group design evaluating the efficacy and safety of 28 days treatment with AZD2066 in patients with painful diabetic neuropathy (PDN).

Target subject population and sample size

Eligible patients (male or non-fertile female patients aged 18 to 80, inclusive), with a clinically established diagnosis of PDN and a NRS pain intensity score of ≥4 to ≤9, inclusive, at enrollment (7-day recall) and at randomisation (average of 5-day 12-hour recall) were enrolled.

With 40 patients treated with AZD2066 and 40 patients receiving placebo, there was 90% power for AZ2066 to be statistically significantly better than placebo at a significance level of 10% (1-sided). The sample size was calculated to test the null hypothesis H0: no difference between AZD2066 and placebo with regard 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 (IP) and comparator(s): dosage, mode of administration and batch numbers

The IP, AZD2066 and/or placebo, was taken orally. It was taken once daily (QD), in the morning together with breakfast. The IP was to be taken at approximately the same time of the day during the study period. Rescue medication (paracetamol/acetaminophen) was provided by investigators. The IP was administered under the supervision of the study personnel during the inpatient period at Visit 3 after the patient was randomized to 1 of the 2 treatment arms: 1) AZD2066 12 mg Days 1-4 and 18 mg Days 5-28; and 2) placebo. The total treatment period was 28 days. Individual batch numbers and further information are included in the CSR.

Duration of treatment

The study comprised of 3 phases: an enrollment phase (including washout period and baseline period), a treatment phase (inpatient and outpatient), and a follow-up phase. Patients randomized to treatment with AZD2066 received AZD2066 12 mg from Days 1 to 4 and 18 mg from Days 5 to 28. The treatment period consisted of an initial 10-day inpatient phase followed by an 18-day outpatient phase.

Statistical methods

In general, all efficacy, safety and PK (plasma concentrations of AZD2066) variables are presented using descriptive statistics and graphs as appropriate. Continuous variables are presented with descriptive statistics (n, mean, standard deviation [SD], median, min, max), within treatment group.

The primary efficacy statistical test was 1-sided with a significance level of 10%. Where appropriate, secondary efficacy analyses reported 1-sided nominal p-values to aid the

interpretation of results. Where appropriate, model-based point estimates are presented together with their 80% confidence intervals (CIs).

Subject population

A total of 334 patients were enrolled in the study. Of these, 127 were randomized to AZD2066 (62 patients) and placebo (65 patients). Of the 127 patients randomized, 83.5% (106/127 patients) completed treatment and 16.5% (21/127 patients) discontinued treatment. Five patients (8.1%) in the AZD2066 group and 2 patients (3.1%) in the placebo group experienced AEs leading to the discontinuation of IP.

In general, demographic characteristics were similar between the AZD2066 and placebo groups. Overall, the mean age was 58.1 years (range 37 to 78 years), and 55.1% of patients were male and 44.9% were female. Most patients (61.4%) were White. Baseline NRS pain intensity scores were slightly higher for the placebo group than the AZD2066 group (~25% between 8-9 for placebo compared with 18% for AZD2066) and lower for the AZD group (~26% between 4-6 for AZD compared with ~12% for placebo).

Summary of efficacy results

Primary efficacy

The primary efficacy outcome variable was the change in mean NRS (pain intensity) scores from baseline to the last 5 days on treatment. Higher NRS scores indicate higher levels of pain intensity, thus, a negative change from baseline indicates a reduction (or improvement) in pain intensity.

In the Primary Per Protocol (PPP) analysis set using the last observation carried forward (LOCF) approach, the mean NRS scores declined from baseline to the last 5 days on treatment for both AZD2066 and placebo, indicating a reduction in pain intensity in both groups. However, the difference (0.19) (2-sided 80% CI: -0.35, 0.73) in mean change from baseline in NRS scores between AZD2066 and placebo was not statistically significant at the 1-sided significance level of 0.1 (1-sided p=0.675). That is, patients treated with AZD2066 did not experience a significantly greater reduction in pain intensity than the placebo-treated patients.

Secondary efficacy

There were no statistically significant differences in the response rates between AZD2066 and placebo based on the NRS (≥30%, ≥50% decrease) and PGIC scores, and in the BPI-SF or MPQ-SF scores.

Summary of pharmacokinetic results

The achieved exposure in the study with a concentration at steady state (C_{ss}) of approximately 2100 nmol/L in the study as a whole was approximately 60% higher than predicted for this age-group based on data in healthy volunteers using this formulation. A possible explanation for this is that the diabetic disease has a negative impact on the ability to eliminate AZD2066. An effect of smoking (current nicotine use) on clearance was identified suggesting that

induction of elimination occurs in smokers. The clearance in smokers was 74% higher compared to non-smokers. The magnitude of the effect should be interpreted with caution due to the limited number of smokers included in the study.

Summary of safety results

AZD2066 demonstrated acceptable safety and tolerability. There were no deaths in this study. Adverse events and recognition of study-specific discontinuation criteria were the most common reasons for discontinuation from the study. Two serious adverse events (SAEs) reported during the study (1 each in the AZD2066 and placebo group) were unrelated to the IP as judged by the investigator. The highest rate of AE-related discontinuations was seen in the AZD2066 group (8%). Headache, dizziness, diarrhoea and arthralgia were the most commonly reported AEs. These AEs were seen in both treatment groups. Seven patients in the AZD2066 group experienced psychiatric AEs while there were none in the placebo group. Of these, only 2 patients with psychiatric AEs discontinued from the study. There were no significant trends in hepatic function tests, ECG, or vital signs.