AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D2600C00005
Edition Number	1
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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 AZD2423 Compared to Placebo in Patients with Painful Diabetic Polyneuropathy

Study dates: First subject enrolled: 20 September 2010
Last subject last visit: 6 June 2011

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 at totally 20 centres in following countries: United Stated (US) (13 active centres) and Canada (7 active centres).

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**	
1. To investigate the analgesic efficacy of AZD2423 compared with placebo after 28 days of oral administration in patients with PDN.	Primary variable: Change from baseline in mean NRS - Average Pain score.[a] Secondary variable: Change from baseline in mean NRS - Worst Pain score.[a]	Efficacy
Secondary	**Secondary**	
1. To investigate the responder rate of patients receiving AZD2423 compared to placebo in patients with PDN.	Responder rate (%), where responders are defined as patients with: a) NRS – Average Pain score reduced by ≥30% from baseline; b) NRS - Average Pain score reduced by ≥50% from baseline; c) NRS –Worst Pain score reduced by ≥30% from baseline; d) NRS - Worst Pain score reduced by ≥50% from baseline; e) at least "much improved" on PGIC; f) at least "much improved" on IOC-Pain	Efficacy
2. To investigate the analgesic efficacy of AZD2423 on different components of pain compared to placebo in patients with PDN.	Change from baseline in NPSI total score and NPSI subscales score	Efficacy
3. To investigate the effect of AZD2423 on different functional consequences of pain compared to placebo in patients with PDN.	Change from baseline in NRS-Pain Interference on Sleep and in NRS-Pain Interference on Activities, IOC –Physical Activity	Efficacy
4. To investigate the pharmacokinetics of AZD2423 in patients with PDN.	C_{max}, $C_{ss,av}$.	Pharmaco-kinetic
5. To investigate the safety and tolerability of AZD2423 in patients with PDN.	Adverse events, laboratory variables, vital signs (pulse and blood pressure), ECG, C-SSRS	Safety
Exploratory		
1. To explore the effect of AZD2423 versus placebo upon stimulus-evoked pain (mechanical allodynia and/or punctate hyperalgesia). Applies only to patients with stimulus-evoked pain.	Change from baseline in NRS-Mechanical Hyperalgesia and NRS-Mechanical Allodynia	Efficacy
2. To explore the effects of AZD2423 compared with placebo on the consumption of rescue medication.	Number of patients using rescue medication, mean daily intake (mg) of rescue medication, change in total intake (mg) of rescue medication from five-day baseline to last 5 days of treatment	Efficacy
3. To explore the relationship between AZD2423 plasma concentration and efficacy and safety variables [b].	C_{max}, $C_{ss,av}$, relevant efficacy and safety variables	Pharmaco-kinetic
4. To investigate levels of ligand CCL2 in plasma.	Levels of CCL2 in plasma	Biomarkers

Objectives	Outcome variables	Type
5. To explore whether AZD2423 has any effect on glucose control in diabetes type II [b].	Fasting glucose, C-peptide, insulin, FFA, HbA1c, TG, LDL, HDL, total cholesterol	Safety
6. To collect and store plasma and blood samples for future, possible exploratory research aimed at investigation into exploratory biomarkers related to disease and/or neuropathy and/or neuropathic pain and/or inflammation and/or biomarkers related to mechanism of action [b].	Blood sample for future, possible exploratory research aimed at investigation of exploratory biomarkers	Biomarkers
7. To explore the pharmacogenetics of AZD2423 by genotyping in blood [b].	Blood sample for genetic research	Pharmaco-genetics

CSR Clinical Study Report; C-SSRS Columbia Suicide Severity Rating Scale; CSP Clinical study protocol; FFA Free Fatty Acids; HDL High-Density Lipoprotein; IOC Impression of Change; LDL Low-Density Lipoprotein; NRS Numerical Rating Scale; NPSI Neuropathic Pain Symptom Inventory; PGIC Patient Global Impression of Change; TG Triglyceride

[a] Baseline score is based on assessments at Day –5 to Day –1. Endpoint score is based on assessments at Day 24 to Day 28.

[b] Reported separate from this CSR.

Study design

This was a phase IIa, double-blind, randomised, parallel-group, multi-centre study to evaluate the analgesic efficacy of 28-day oral administration of AZD2423 compared with placebo in patients with Painful Diabetic Polyneuropathy (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 with a duration of 3 months to 5 years and a NRS pain intensity score of ≥4 to ≤9, inclusive, at enrolment (7-day recall) and at randomisation (average of 5-day 12-hour recall) were enrolled.

The sample size calculation in this study was done to demonstrate superior efficacy of AZD2423 over placebo and was calculated with regards to the primary outcome variable. The appropriate sample size was attained by a t-test procedure assuming a clinically relevant difference of 1.2 units from placebo and a standard deviation (SD) of 2.1. With a power of 90% and an alpha level of 0.10 (one-sided) the study needed a sample size of 40 evaluable patients per group (120 in total). In order to obtain 120 evaluable patients, 134 patients were randomised into the study. Patients were randomly assigned to blinded treatment in a 1:1:1 ratio to AZD2423 20 mg, AZD2423 150 mg or placebo.

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

The investigational product (AZD2423 or placebo) was taken orally once daily, in the morning, for 28 days. The investigational product was to be taken at approximately the same time each day during the treatment period, with water, with or without food. The patient was to take 4 tablets at each administration: 3 tablets from the bottle labelled “AZD2423 tablets 50 mg or Placebo” and 1 tablet from the bottle labelled “AZD2423 tablets 20 mg or Placebo”.

The investigational products were manufactured at AstraZeneca R&D Charnwood. The batch numbers were 10-003799AZ, 10-004710AZ and 10-005854AZ for AZD2423 20 mg; 10-003900AZ, 10-005266AZ and 10-005954AZ for AZD2423 150 mg; 10-004415AZ, 10-004661AZ and 10-005777AZ for placebo.

Duration of treatment

The patients received treatment for 28 days.

Statistical methods

In general, all efficacy, safety and pharmacokinetics variables are presented using descriptive statistics and graphs as appropriate. Continuous variables are presented with descriptive statistics (n, mean, SD, median, min, max), within treatment group and within dose. Categorical variables are summarized in frequency tables (number of patients and percentage), by treatment group and dose. Data is also presented in individual patient listings.

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). The primary objective was analysed using mixed model with repeated measurements (MMRM).

Subject population

A total of 355 patients were enrolled in the study. Of these, 134 patients were randomised: 45 patients to AZD2423 20 mg, 48 to AZD2423 150 mg and 41 to placebo. Of the 134 patients randomised, 82.1% (110 patients) completed treatment and 17.9% (24 patients) discontinued treatment.

In general, demographic characteristics were similar among the AZD2423 and placebo groups. Overall, the mean age was 58 years (range 34 to 77 years), 51.5% of patients were male and 48.5% were female. Most patients (61.9%) were White. Mean baseline NRS-Average pain scores (5-day mean, 12 h recall twice daily) at randomisation were 6.4 for AZD2423 20 mg group, 6.1 for AZD2423 150 mg group, and 6.6 for the placebo group.

Summary of efficacy results

The mean NRS-Average Pain scores declined from baseline to end of treatment in all three groups, indicating a reduction in pain intensity. The mean change from baseline to end of treatment was -1.50 in the AZD2423 20 mg group, -1.35 in the AZD2423 150 mg group, and -1.61 in the placebo group. The difference in mean change in NRS-Average Pain scores from baseline to last 5 days of the treatment period (Day 24 to Day 28) between either of the AZD2423 groups and the placebo group was not statistically significant (adjusted 1-sided p=0.74 for the AZD2423 20 mg and 150 mg groups).

The results of the responder rates (based on NRS-Average Pain, NRS-Worst Pain, PGIC and IOC-Pain scores) and effect on pain interference on sleep and activity (as assessed by NRS -

Pain Interference on Sleep, NRS - Pain Interference on Activities, and IOC –Physical Activity) were consistent with the results of the primary variable.

In the AZD2423 150 mg group, there was a significant improvement (reduction) of the NPSI total score compared to placebo (1-sided p=0.06). For all NPSI subscores (evoked pain, pressing [deep] spontaneous pain, paroxysmal pain, paraesthesia/dysesthesia and burning [superficial] spontaneous pain), the reduction in pain was numerically higher for both AZD2423 dose groups than for placebo. The reduction was statistically significantly higher for AZD2423 150 mg compared to placebo for 3 subscores: evoked pain (1-sided p=0.05), pressing (deep) spontaneous pain (1-sided p=0.06) and paraesthesia/dysesthesia (1-sided p=0.06).

There were no obvious treatment-related effects on NRS-Mechanical Allodynia and NRS-Mechanical Hyperalgesia scores. Rescue medication intake was similar among the three treatment groups.

Summary of pharmacokinetic results

Median average plasma concentration at steady state ($C_{ss,av}$) was approximately 12 nmol/L (range 5.0-19.3 nmol/L) for the AZD2423 20 mg dose group and 110 nmol/L (range 60.0-187.2 nmol/L) for the AZD2423 150 mg dose group. Median maximum concentration (C_{max}) was approximately 24 nmol/L (range 9.9-47.8 nmol/L) for the AZD2423 20 mg group and 270 nmol/L (range 89.8-649.8 nmol/L) for the AZD2423 150 mg group.

Summary of pharmacodynamic results

CCL2 plasma levels increased from baseline following treatment with AZD2423. The observed increase of CCL2 was larger in the AZD2423 150 mg group compared to the AZD2423 20 mg group. The plasma CCL2 levels decreased rapidly after stopping AZD2423 treatment.

Summary of safety results

There was 1 death (sudden cardiac death) during the study, not considered by the investigator as causally related to the investigational product. Three patients (all in AZD2423 20 mg group) had 4 serious adverse events (SAEs), including 1 death, during the study. One of the patients had an SAE (Clostridium difficile colitis) that was judged by the investigator as causally related to investigational product. In total, 9 patients experienced AEs leading to discontinuation of investigational product (DAEs): 4 patients (9.1%) in the AZD2423 20 mg group, 3 patients (6.4%) in the AZD2423 150 mg group, and 2 patients (4.9%) in the placebo group.

The overall frequency on AEs was similar in the AZD2423 and placebo groups. The incidence of patients with any AE was 21 patients (51.2%) in the placebo group, as compared to 15 patients (34.1%) in the AZD2423 20 mg group and 17 patients (36.2%) in the AZD2423 150 mg group. Gastrointestinal disorders were reported by 3 patients (6.8%) in the AZD2423 20 mg group, 5 patients (10.6%) in the AZD2423 150 mg group and 7 patients (17.1%) in the

placebo group. Infections and infestations were reported by 3 patients (6.8%) in the AZD2423 20 mg group, 5 patients (10.6%) in the AZD2423 150 mg group and 2 patients (4.9%) in the placebo group. Most common AEs in the AZD2423 groups were headache, dizziness, nausea and pyrexia.

No clinically important treatment-related changes were identified in laboratory parameters, vital signs, ECG variables, physical examination findings, weight or BMI.