AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D2600C00012
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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 Posttraumatic Neuralgia

Study dates: First subject enrolled: 06 October 2010
Last subject last visit: 03 April 2012

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

The objectives and variables of this study are summarised in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To investigate the analgesic efficacy of AZD2423 compared with placebo after 28 days of oral administration in patients with PTN.	Primary variable: Change from baseline in mean NRS-Average Pain score.[a] Secondary variable: Change from baseline in mean NRS-Worst Pain score.[a]
Secondary	Efficacy	1. To investigate the responder rate of patients receiving AZD2423 compared to placebo in patients with PTN.	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 PTN.	Change from baseline in NPSI total score; Change from baseline in NPSI subscales score

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Priority	**Type**	**Description**	**Description**
	Efficacy	3. To investigate the effect of AZD2423 on different functional consequences of pain compared to placebo in patients with PTN.	Change from baseline in NRS - Pain Interference on Sleep; Change from baseline in NRS-Pain Interference on Activities; IOC-Physical Activity.
	PK	4. To investigate the PK of AZD2423 in patients with PTN.	C_{max}, $C_{ss, av}$
	Safety	5. To investigate the safety and tolerability of AZD2423 in patients with PTN.	Adverse events, Laboratory variables, Vital signs: pulse and blood pressure, ECG, C-SSRS.
Exploratory	Efficacy	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 Change from baseline in NRS-Mechanical Allodynia Change from baseline in Area of 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 5-day baseline to last 5 days of treatment.
	PK[b]	3. To explore the relationship between AZD2423 plasma concentration and efficacy and safety variables.	This will be reported separately from this CSR.
	Biomarkers	4. To investigate levels of ligand CCL2 in plasma.	Levels of CCL2 in plasma.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Biomarkers[c]	5. 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.	Blood sample for future, possible exploratory research aimed at investigation into exploratory biomarkers.
Pharmacogenetic	Pharmacogenetic[d]	To explore the pharmacogenetics of AZD2423 by genotyping in blood.	Blood sample for genetic research.

[a] Baseline score was based on assessments at Day –5 to Day –1. Endpoint score was based on assessments at Day 24 to Day 28.
[b] Exploratory objective 3: The relationship between AZD2423 plasma concentration and efficacy variables was explored, however, this will be reported separately and is not included in the CSR. The relationship between AZD2423 plasma concentration and safety variables was not explored.
[c] Exploratory objective 5 will be reported separately and is not included in the CSR.
[d] The pharmacogenetic objective will be reported separately and is not included in the CSR.
CCL2 Chemokine (C-C motif) ligand 2; CSR Clinical Study Report; C-SSRS Columbia Suicide Severity Rating Scale; CSP Clinical study protocol; IOC Impression of Change; NRS Numerical Rating Scale; NPSI Neuropathic Pain Symptom Inventory; PGIC Patient Global Impression of Change; PK Pharmacokinetic; PTN Post traumatic Neuralgia.

Study design

This was a Phase IIa, double-blind, randomised, parallel-group, multi-centre study to evaluate the analgesic efficacy of 28 days' oral administration of AZD2423 compared with placebo in patients with posttraumatic neuralgia (PTN).

Target subject population and sample size

Male or non-pregnant and non-lactating female patients aged 18 to 80 years, inclusive, with neuropathic pain due to peripheral nerve injury caused by trauma or surgery (duration of pain 3 months to 5 years) and a NRS pain intensity score of ≥4 to ≤9 at enrolment (7-day recall) and at randomisation (5-day mean 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 assuming an anticipated difference of 1.2 units from placebo and a standard deviation of 2.1. With a power of 90% and an alpha-level of 0.10 (1-sided) the study needed a sample size of 40 evaluable patients per group (120 in total). In order to obtain 120 evaluable patients, approximately 135 patients were planned to be randomised into the study. Patients were randomly assigned to blinded treatment in a 1:1:1 ratio to receive either AZD2423 20 mg (low dose), AZD2423 150 mg (high dose), or placebo.

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

The investigational product (AZD2423 and placebo) was supplied as 50 mg and 20 mg strength tablets with a matching placebo for oral administration. AZD2423 or matching placebo was to be taken orally with water, with or without food, once daily, in the morning for 28 days at approximately the same time each day, during the treatment period.

The investigational products were manufactured at AstraZeneca R&D Charnwood, UK. The batch numbers were 10-003799AZ, 10-004710AZ, 10-005854AZ, 11-000117AZ, and 11-001008AZ for AZD2423 20 mg; 10-003900AZ, 10-004767AZ, 10-005954AZ, 11-000173AZ, 11-001058AZ for AZD2423 50 mg; and 10-004415AZ, 10-004661AZ, 10-005777AZ, 11-000105AZ, 11-001007AZ for the placebo group.

Duration of treatment

All randomised patients were to receive treatment for 28 days.

Statistical methods

In general, all efficacy, safety, and pharmacokinetic (PK) analyses are presented using descriptive statistics and graphs as appropriate. Continuous variables are presented with descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum), within treatment group, and within dose. Categorical variables are summarised in frequency tables (number of patients and percentage), by treatment group and dose. Data are also presented in individual patient listings.

The primary efficacy variable - change from baseline to Day 24 to Day 28 on treatment in Numerical Rating Scale (NRS)-Average Pain, was analysed using a linear mixed model with repeated measures (MMRM). The analysis was performed on the modified intention-to-treat (mITT) analysis set and on observed cases (OC). As a consistency check of the results, the analysis was also run on the per-protocol (PP) analysis set.

All statistical tests were 1-sided with a significance level of 10%. Where appropriate, secondary efficacy analyses reported the nominal p-values at 10% level to aid the interpretation of results. No adjustments for multiplicity were made for these secondary analyses. Where appropriate, model-based point estimates were presented together with their 80% confidence intervals.

Subject population

Disposition

A total of 274 patients were enrolled in the study. Of these, 133 patients were randomised: 48 patients to the AZD2423 20 mg group, 41 patients to the AZD2423 150 mg group, and 44 patients to the placebo group.

The majority of the patients randomised (126 [94.7%]) completed the study. Seven (5.3%) patients discontinued from the study. The most common reason for discontinuing from study was 'Withdrawal by Subject', reported in 5/133 (3.8%) patients. The other reasons or discontinuation from study were 'Adverse event' reported in 1 patient from the AZD2423 150 mg group, and 'Other reason' (patient withdrew from study due to non availability of study nurse) reported in 1 patient from the placebo group. All the 133 patients randomised were included for safety and mITT analyses.

The disposition of patients in this study is summarised in Table S2.

Table S2 Patient disposition (All enrolled patients)

	Number (%) of patients			
	AZD2423 20 mg	**AZD2423 150 mg**	**Placebo**	**Total**
Patients enrolled	NA	NA	NA	274
Patients randomised[a]	48	41	44	133(48.5%)
Patients not randomised[a]	NA	NA	NA	141(51.5%)
Patients who received treatment[b]	48	41	44	133(100.0%)
Patients who completed study[b]	47	39	40	126(94.7%)
Patients who discontinued study[b]	1	2	4	7(5.3%)
STUDY DISCONTINUED DUE TO WITHDRAWAL BY SUBJECT	1	1	3	5(3.8%)
STUDY DISCONTINUED DUE TO ADVERSE EVENT	0	1	0	1(0.8%)
STUDY DISCONTINUED DUE TO OTHER REASON	0	0	1	1(0.8%)

[a] The denominator of the percentage is total number of patients enrolled.
[b] The denominator of the percentage is total number of patients randomised.

The demographic characteristics were similar between the AZD2423 and placebo groups, except for a slightly higher proportion of females in the AZD2423 20 mg group as compared with the AZD2423 150 mg, and placebo group. Overall, the mean age was 53.1 years (range 21 to 73 years); 53.4% of patients were male, and 46.6% were female. Most patients (99.2%) were White (only 1 patient was Black or African American).

The overall mean baseline NRS-Average Pain score (5-day mean, 12-hour recall twice daily) at randomisation was 5.9. Mean baseline NRS-Average Pain scores were 6 for placebo, 6 for AZD2423 20 mg and 5.7 for AZD2423 150 mg. NRS-Average Pain scores (7-day recall) at enrolment were 6.2 for the placebo group, 6.2 for AZD2423 20 mg and 5.8 for AZD2423 150 mg group. The NRS-Average Pain scores at enrolment and randomisation were comparable between the 3 treatment groups.

Summary of efficacy results

Primary variable: Change in mean NRS-Average Pain score from baseline to end of treatment

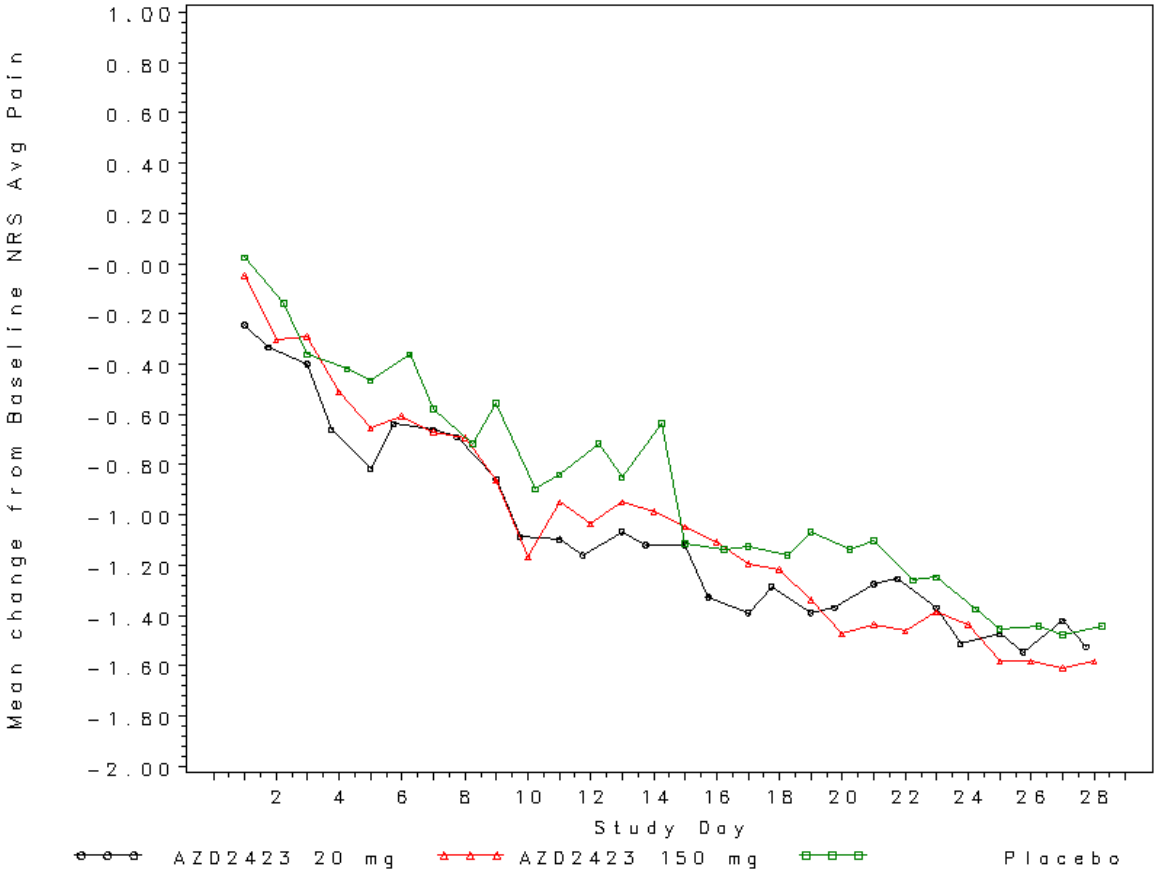
The mean NRS-Average Pain scores declined from baseline to end of treatment in all 3 treatment groups, indicating a reduction in pain intensity. The mean change from baseline to end of treatment was -1.54 in the AZD2423 20 mg group, -1.53 in the AZD2423 150 mg group, and -1.44 in the placebo group.

In the mITT analysis set using the MMRM approach, the difference in mean change from baseline in NRS-Average pain scores between either of the AZD2423 groups and the placebo group was not statistically significant (adjusted 1-sided p-value was 0.50 for the AZD2423 20 mg group and 0.36 for the AZD2423 150 mg group).

The results for the primary variable were confirmed by the analyses based on data from the Per-Protocol analysis set (1-sided p-value 0.61 in the AZD2423 20 mg group, and 0.43 in the AZD2423 150 mg group).

Mean change from baseline in daily NRS-Average Pain score over time for AZD2423 dose groups and placebo is presented in Figure 1.

Figure 1 **Mean change from baseline in daily NRS - Average Pain scores over time from Days 1 to 28 AZD2423 and placebo groups (mITT analysis set, LOCF)**



LOCF Last observation carried forward; mITT Modified intention-to-treat; NRS Numerical Rating Scale.

Secondary variables:

The difference in mean change from baseline in NRS-Worst Pain scores between either of the AZD2423 groups and the placebo group was not statistically significant. 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.

The mean Neuropathic Pain Symptom Inventory (NPSI) total scores declined from baseline to end of treatment for the AZD2423 and placebo groups, indicating a reduction in pain severity in all 3 groups. The reduction was greater for the AZD2423 150 mg group (−16.58), than for placebo (−9.80) and AZD2423 20 mg (−8.82) groups. The change from baseline to Day 28 in the NPSI total score was not statistically significant in any of the AZD2423 groups as

compared with placebo (1-sided p-value of 0.52 for the AZD2423 20 mg group and 0.10 for the AZD2423 150 mg group).

Change from baseline to end of treatment in NPSI subscores were non-significant for most of the sub scales except Paroxysmal pain (item 5,6) and Paraesthesia/Dysesthesia (item 11,12) where AZD2423 150 mg was statistically significant as compared to placebo (1-sided p-value 0.05 for Paroxysmal pain and 1-sided p-value of 0.04 for Paraesthesia/Dysesthesia).

Summary of pharmacokinetic results

Based on the plasma concentration data, the intended mean exposure was reached in both AZD2423 dose groups.

Median average plasma concentration at steady state ($C_{ss,av}$) was 12 nmol/L (10^{th} and 90^{th} percentile 7.3 to 17 nmol/L) for the AZD2423 20 mg group and 110 nmol/L (10^{th} and 90^{th} percentile 84 to 150 nmol/L) for the AZD2423 150 mg dose group.

Median maximum concentration (C_{max}) was approximately 18 nmol/L (10^{th} and 90^{th} percentile 11 to 31 nmol/L) for the AZD2423 20 mg group and 270 nmol/L (10^{th} and 90^{th} percentile 140 to 350 nmol/L) for the AZD2423 150 mg group.

Summary of pharmacodynamic results

Chemokine (C-C motif) ligand 2 (CCL2) plasma levels increased with increased dose of AZD2423.

Summary of safety results

A total of 66 patients experienced at least 1 AE in any category during the study: 27 patients in the AZD2423 20 mg group, 20 patients in the AZD2423 150 mg group, and 19 patients in the placebo group. There were no AEs with outcome of death, or SAEs reported during the study. There were no AEs, classified as Other significant adverse events (OAEs) that were reported during the study.

The incidence of patients experiencing any AE was slightly higher in the AZD2423 20 mg group (56.3%) as compared with the AZD2423 150 mg and placebo groups (48.8% and 43.2%, respectively).

Overall, the highest incidence of AEs was observed in the SOCs: “gastrointestinal disorders”, “infections and infestations”, “musculoskeletal and connective tissue disorders”, and “nervous system disorders”. Most common AEs in the AZD2423 groups were headache, nausea, diarrhoea, and nasopharyngitis. Incidence of headache, nausea, and diarrhoea was higher in the AZD2423 150 mg group (14.6%, 9.8%, and 7.3%, respectively), whereas, the incidence of nasopharyngitis was higher in the AZD2423 20 mg and placebo groups (10.4% and 9.1%, respectively). Asthenia was reported in 3 patients (6.3%) in the AZD2423 20 mg group only. Most AEs were mild or moderate in intensity, except for 1 AE (Sleep disturbances) in the AZD2423 20 mg group which was severe in intensity. The AE was resolved by the last

documented visit. Headache, nausea, and diarrhoea were the most commonly occurring causally related AEs in the AZD2423 groups.

No major safety or tolerability concerns related to AZD2423 were identified from AE reporting, laboratory parameters, vital signs, electrocardiogram variables, or physical examination findings.