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Evaluation of a novel chemokine receptor 2 (CCR2)-antagonist in painful diabetic polyneuropathy

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HIGHLIGHTS

- CCR2-antagonists are effective in preclinical models of neuropathic pain.
- A novel CCR2-antagonist, AZD2423, was studied in painful diabetic polyneuropathy.
- Biomarker data in patients suggested that AZD2423 interacted with the target CCR2.
- AZD2423 was no better than placebo on the primary and most secondary pain variables.
- However, neuropathic pain symptom inventory (NPSI) data showed possible effects on certain sensory components of pain.

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ABSTRACT

Background and aims: Preclinical data suggest that the chemokine receptor 2 (CCR2) is involved in the pathophysiology of neuropathic pain through modulation of neuronal excitability, synaptic transmission and activation of spinal cord microglia. CCR2-antagonists have shown to be effective in preclinical models of neuropathic pain. The aim of this study was to evaluate the analgesic efficacy, safety and tolerability of a novel CCR2-antagonist, AZD2423, in patients with painful diabetic neuropathy (PDN).
Methods: This was a double-blind, randomized, parallel-group, multi-center study in patients with symmetric distal sensory polyneuropathy due to type 1 or 2 diabetes and duration of neuropathic pain between 3 months and 5 years. Concomitant treatment with neuropathic pain medications (e.g. anticonvulsants, tricyclic antidepressants, serotonin-noradrenaline uptake inhibitors, opioids, topical lidocaine or capsaicin) was not allowed. 134 patients with PDN were equally randomized to 28 days oral administration of 20 mg AZD2423, 150 mg AZD2423, or placebo. The primary efficacy variable was the change of average pain score from 5-days baseline to the last 5 days of treatment, measured with numerical rating scale (NRS, 0–10). The secondary efficacy measures included NRS worst pain scores, patient global impression of change, pain interference on sleep and activity, and neuropathic pain symptom inventory (NPSI).
Results: The change of NRS average pain score was not significantly different between treatment groups (AZD2423 20 mg: −1.50; AZD2423 150 mg: −1.35; placebo: −1.61). The NPSI total score and three out of five subscores (evoked pain, pressing/deep pain and paresthesia/dysesthesia) tended to be reduced more by AZD2423 150 mg than by placebo. No other secondary efficacy variables differed between treatment groups. The frequency and type of adverse events for AZD2423 were similar to placebo. The achieved plasma levels of AZD2423 in the two dose groups were in line with predictions from pharmacokinetic data previously obtained in healthy volunteers. Dose-dependent increase of plasma levels of the ligand of CCR2 (CCL2; chemokine ligand 2) and decrease of the mean levels of monocytes (−27% by AZD2423 150 mg) suggested that the administrated doses of AZD2423 interacted with the CCR2 target.
Conclusion: The CCR2-antagonist AZD2423 showed no analgesic efficacy in PDN based on NRS average pain scores and global and functional pain outcome measures. The NPSI data suggested possible effects on certain sensory components of pain. There were no major safety or tolerability concerns.

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Implications: Treatment with a CCR2-antagonist does not have a clinically important analgesic effect in an overall PDN population.

1. Introduction

The chemokine receptor 2 (CCR2) has been a target of interest for treatment of chronic inflammatory diseases such as rheumatoid arthritis and multiple sclerosis [1–4]. Recent preclinical studies have shown that CCR2 and its ligand CCL2 (chemokine ligand 2) also can be involved in the pathophysiology of neuropathic pain [5], e.g. through increased neuronal excitability [6–9], synaptic release of CCL2 [10,11] and/or activation of spinal cord microglia [12] after peripheral nerve injury. Activation of spinal cord microglia mediates pain behavior in the streptozotocin-induced mouse model of diabetic neuropathy [13–15].

AZD2423 is a new chemical entity which is a potent, selective and reversible antagonist of the human CCR2 (unpublished data, AstraZeneca R&D). Due to species differences in CCR2 characteristics, preclinical studies have been conducted with a rat-specific CCR2-antagonist tool compound, which has showed efficacy in rat models of neuropathic pain [16].

Data from Phase I studies in healthy volunteers have shown acceptable safety, tolerability and pharmacokinetics of AZD2423 (unpublished data, AstraZeneca R&D). In a multiple ascending dose study, daily doses of 150 mg for 12 days were well tolerated, whereas at 300 mg, mild to moderate gastrointestinal side effects (nausea, vomiting, loose stools, abdominal pain) occurred in most subjects.

Diabetic polyneuropathy is one of the most common causes of neuropathic pain and the need for new treatment options is high, both regarding efficacy, safety and tolerability. This study was conducted to investigate the hypothesis that treatment with AZD2423 reduces neuropathic pain more than placebo in patients with painful diabetic neuropathy (PDN).

2. Methods

The study was conducted at 13 centers in the United States and 7 centers in Canada from September 2010 to June 2011. The study has been registered on clinicaltrials.gov; identifier NCT01201317.

2.1. Study population

Male or female patients of non-childbearing potential 18–80 years of age with pain due to diabetic polyneuropathy and duration of pain between 3 months and 5 years were included. A diagnosis of symmetric distal sensory polyneuropathy due to type 1 or 2 diabetes was required. The diagnostic criteria for polyneuropathy and neuropathic pain were specified at an investigator meeting. Typical distribution of sensory symptoms (e.g. numbness, tingling, or burning pain) and signs (abnormal sensation of touch, pin-prick, skin temperature or vibration) distally and symmetrically in the extremities was required. The distribution of pain should correspond to the distribution of other polyneuropathic sensory symptoms and signs. Ongoing peripheral arterial disease, skin ulcers or amputation was an exclusion criterion. The anti-diabetic regimen should have been stable for three months before enrolment and HbA1c $\leq$ 10%. Concomitant treatment with neuropathic pain medications (e.g. anticonvulsants, tricyclic antidepressants, serotonin-noradrenaline uptake inhibitors, opioids, topical lidocaine or capsaicin) was not allowed and had to be washed out at least 10 days in advance of the start of baseline pain recordings. Patients with other pain conditions that may confound assessment of neuropathic pain, patients with prior treatment of neuropathic pain with neurolytic therapy, intrathecal pump, spinal cord stimulator or neurosurgery, and patients with a history of treatment failure with $\geq$3 adequate trials of medications used to treat neuropathic pain, were excluded. The following infection-related exclusion criteria were also applied: chest X-ray or QuantiFERON® – TB Gold suggesting active or latent tuberculosis; immunization with live vaccine within the previous 3 months, for other vaccines within 30 days prior to randomization; history of latent, chronic, or recurrent infections or patients at risk of infection (surgery, trauma or significant infection, history of skin abscesses within 90 days prior to enrolment).

2.2. Standard protocol approvals, registration and patient consents

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). The clinical study protocol and the informed consent form were approved by the Independent Ethics Committee for each study site as appropriate. Informed consent was obtained from all subjects prior to initiation of the study.

2.3. Study design

This was a phase 2a, double-blind, randomized, parallel-group, multi-center study to evaluate the analgesic efficacy of 28 days oral administration of AZD2423 compared with placebo in patients with PDN. Baseline pain intensity at randomization, based on 5 days mean NRS (numerical rating scale; 0–10) had to be between 4 and 9. Patients were randomly assigned to blinded treatment in a 1:1:1 ratio to AZD2423 20 mg, AZD2423 150 mg or placebo tablets with approximately 45 patients per treatment group (Fig. 1). Ibuprofen 400 mg, max 1200 mg daily dose, was allowed as rescue medication during the entire study.

2.4. Assessments

Patients rated their perceived "average pain" intensity during the last 12 h on an NRS (0–10) scale every morning and evening from visit 2 to visit 7. The change from 5 days baseline mean NRS to the last 5 days of treatment (Day 24–28) was the primary outcome variable. The secondary outcomes were the change of mean "worst pain" NRS (rated every morning and evening), responder rates based on 30% and 50% reduction of average pain NRS and worst pain NRS, responder rate based on at least "much improved" on 7-item PGIC (patient global impression of change) recorded at visits 4–7, NPSI (neuropathic pain symptom inventory) [17] total score and 5 subscores (evoked pain, pressing [deep] spontaneous pain, paroxysmal pain, paraesthesia/dysesthesia and burning [superficial] spontaneous pain) recorded at visits 3 and 7, daily ratings of pain interference on activities and sleep, and intake of rescue medication. Dynamic mechanical allodynia to brush stimulation and static mechanical allodynia to stimulation with a von Frey hair were assessed at the first visit. The patients rated the intensity of dynamic and static allodynia on an NRS (0–10). Only those subjects that were considered to have either dynamic or static allodynia at the first visit continued to have these measured during study visits

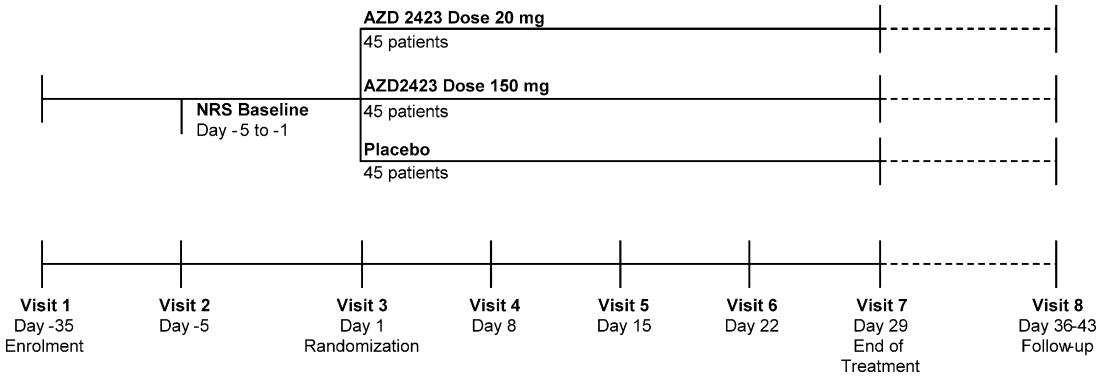

Fig. 1. Study design.

3, 5 and 7. All efficacy measures were recorded by the patient in an electronic diary.

Adverse events (AE) were recorded and reported according to ICH GCP guidelines. The AE were also classified by intensity (mild, moderate, severe) and causality (yes/no). Vital signs (body temperature, blood pressure and pulse rate), ECG, standard clinical chemistry, and hematology tests were monitored at each visit. Blood samples for pharmacokinetic (PK) analysis of AZD2423 were obtained at visits 4–7 and analysis of CCL2 at visits 3–8. Average AZD2423 plasma concentration at steady state ($C_{ss,av}$) and maximum plasma concentration at steady state ($C_{ss,max}$) were calculated based on individual plasma concentration and a population PK model (unpublished data, AstraZeneca R&D).

2.5. Statistical analysis

The sample size was estimated assuming a difference between the treatment groups of 1.2 NRS units and a standard deviation of 2.1. With a power of 90% and an alpha level of 0.10 (one-sided), a sample size of 40 evaluable patients per group (in total 120) was needed.

The primary and secondary efficacy analyses were based on the modified intention-to-treat (mITT) analysis set. The mITT analysis set included all randomized patients who received investigational product until at least Day 5 and had a baseline and at least one post-baseline NRS-average pain assessment. All patients who received at least one dose of randomized investigational product and for whom any post-dose data were available were included in the safety analysis set.

The primary efficacy variable was analyzed using mixed model with repeated measures (MMRM). The analysis was performed on the mITT analysis set and on observed cases using the change from 5-days baseline in NRS daily scores (mean of morning and evening values) as the dependent variable. The two comparisons of interest were the difference in change from baseline (Day −5 to Day −1) to the last five days of the treatment period (Day 24–28) between each of AZD2423 dose levels versus placebo. To test if AZD2423 reduces pain more than placebo contrasts were defined and estimated through the model. Least square means of the difference (AZD2423–placebo), one-sided p-values and the corresponding 80% two-sided confidence intervals were constructed. A fixed-sequence multiple testing procedure for the two treatment comparisons with respect to the primary variable was used (high dose followed by low dose). Adjusted p-values were calculated for both comparisons. Since this was the first study investigating potential analgesic efficacy of AZD2423, the alpha level was set to 0.10 (one-sided), in order to optimize the chances to detect an efficacy signal while keeping the sample size down.

The NRS Worst Pain Score and NRS-Pain Interference on Sleep/Activities scales were also analyzed using MMRM. Responder rates were analyzed by means of generalized estimating equations using a logit link function. The NPSI total score was calculated as the sum of the ten item descriptor scores [17]. The subscores were calculated as mean scores of the items belonging to each of the 5 dimensions. The total score and the subscores were analyzed using linear mixed models (ANCOVA). For mechanical allodynia scores, Spearman's rank correlation was used to assess the dependency between values at enrolment and randomization visits.

3. Results

3.1. Patient characteristics

In total, 134 patients were randomized; 45 patients to 20 mg AZD2423, 48 to 150 mg AZD2423 and 41 to placebo (Fig. 2). 110 (82.1%) patients completed the study. 127 patients were evaluable for the primary efficacy analysis and 132 patients for the safety analysis. The demographic and baseline characteristics were generally similar among the treatment groups (Table 1).

3.2. Primary efficacy outcome measure

The change in NRS-average pain score from 5-days baseline to the last 5 days of treatment showed no difference between any of the AZD2423 treatment groups and placebo. 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 (Fig. 3). The difference in mean change from baseline in NRS-average pain scores between AZD2423 20 mg and placebo was 0.23 ($p = 0.74$) and between AZD2423 150 mg and placebo 0.31 ($p = 0.74$).

3.3. Secondary outcome measures

There was no difference in the mean change from baseline of NRS-worst pain scores between AZD2423 20 mg and placebo (0.26, $p = 0.68$) or between AZD2423 150 mg and placebo (0.17, $p = 0.62$).

The percentage of responders, defined as patients with at least 30% reduction of NRS average pain at the last treatment day, were 45%, 35% and 38% in the AZD2423 20 mg, 150 mg, and placebo groups, respectively. The corresponding responder rates, defined as at least 50% reduction of NRS average pain, were 19%, 22%, and 26%. None of these differences were statistically significant. Neither were there any statistically significant differences between treatment groups in responder rates based on 30% or 50% reduction of NRS worst pain, responder rates based

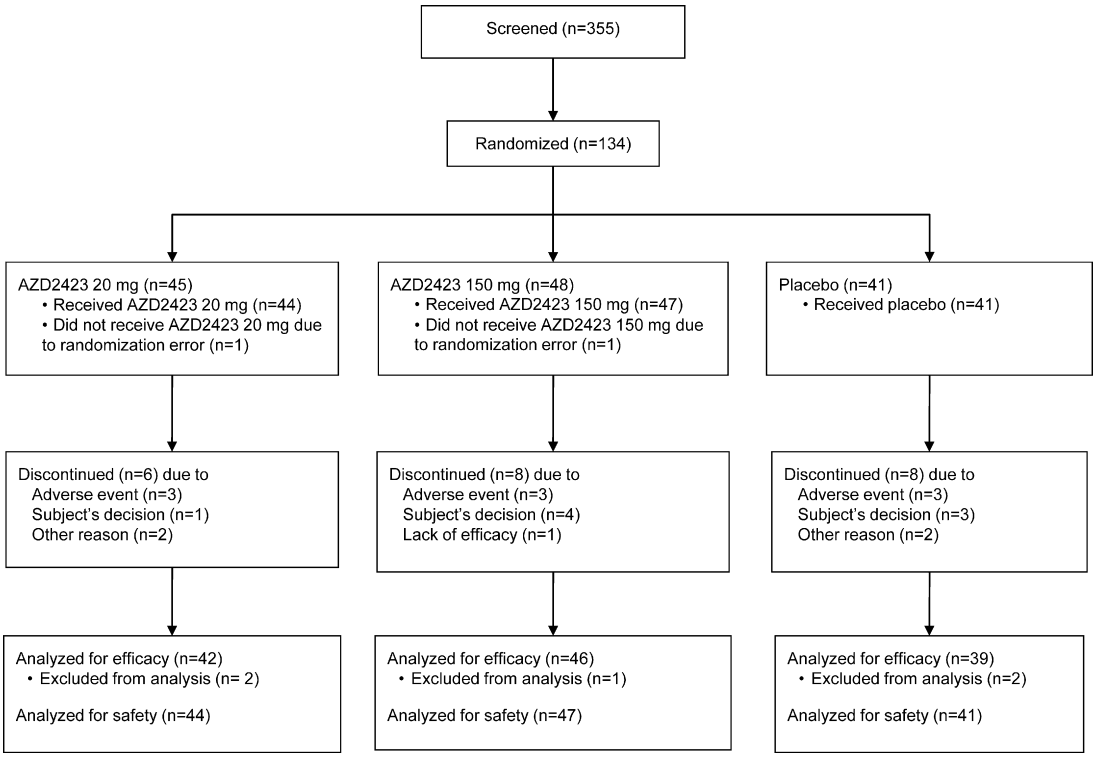

Fig. 2. Subject flow diagram.

on "much improved" on PGIC, mean NRS-Pain Interference on Sleep/Activities scores, nor the amount of intake of rescue medication.

There was a tendency of larger reduction of the mean NPSI total score from Day 1 to Day 29 in the AZD2423 150 mg group (baseline = 49.03; reduction = −15.18) compared with placebo (baseline = 50.48; reduction = −7.82), with $p = 0.06$ (one-sided). There was also a less pronounced numerical reduction of mean NPSI score by AZD2423 20 mg (baseline = 49.53; reduction = -12.76).

For all five NPSI subscores, the reduction in pain was numerically higher for both AZD2423 dose groups than for placebo (Fig. 4). The reduction was most pronounced for AZD2423 150 mg compared to placebo for evoked pain ($p = 0.05$, one-sided), pressing (deep) spontaneous pain ($p = 0.06$, one-sided) and paraesthesia/dysesthesia ($p = 0.06$, one-sided).

A post hoc analysis was made of baseline NPSI total scores and subscores in responders compared with non-responders, defined as patients with/without 30% or 50% reduction of NRS average pain. No significant differences were found of NPSI scores between responders and non-responders.

26% of the randomized patients in the study reported dynamic mechanical allodynia. There was a numerical reduction of mean dynamic allodynia scores in the AZD2423 20 mg (−2.13, s.e. = 0.87) and AZD2423 150 mg groups (−1.56, s.e. = 0.77), whereas there was no change in the placebo (0.00, s.e. = 1.26) group from baseline (randomization) to the last day of treatment. The correlation between values at enrolment and randomization visits was 0.30.

40% of the randomized patients in the study reported static mechanical allodynia. There was a larger numerical reduction of mean static allodynia scores in the AZD2423 150 mg group (−2.19, s.e. = 0.45) compared to the AZD2423 20 mg (−1.19, s.e. = 0.49) and placebo (−1.07, s.e. = 0.71) groups from baseline to the last day of treatment. The correlation between values at enrolment and randomization visits was 0.40.

The effects of AZD2423 on NRS-average and NRS-worst pain scores were also analyzed post hoc for each of the following subgroups: patients with or without dynamic mechanical allodynia at baseline and patients with or without static mechanical allodynia at baseline. No significant differences were found between AZD2423 and placebo in any of these subgroups.

Table 1
Demographic and baseline characteristics.

	Statistic	AZD2423 20 mg	AZD2423 150 mg	Placebo
Age (years)	Mean (SD)	59.6 (8.4)	57.8 (6.9)	56.4 (8.4)
Gender				
Male	*n* (%)	23 (51.1)	25 (52.1)	21 (51.2)
Female	*n* (%)	22 (48.9)	23 (47.9)	20 (48.8)
Race				
White	*n* (%)	32 (71.1)	30 (62.5)	21 (51.2)
Black	*n* (%)	10 (22.2)	12 (25.0)	14 (34.1)
Asian	*n* (%)	1 (2.2)	2 (4.2)	2 (4.9)
Other	*n* (%)	2 (4.4)	4 (8.4)	4 (9.7)
BMI (kg/m^2)	Mean (SD)	36.5 (8.5)	32.7 (6.4)	34.7 (7.3)
NRS baseline	Mean (SD)	6.4 (1.4)	6.1 (1.2)	6.6 (1.0)
HbA1c (%)	Mean (SD)	7.31 (1.17)	7.42 (1.27)	7.22 (1.16)

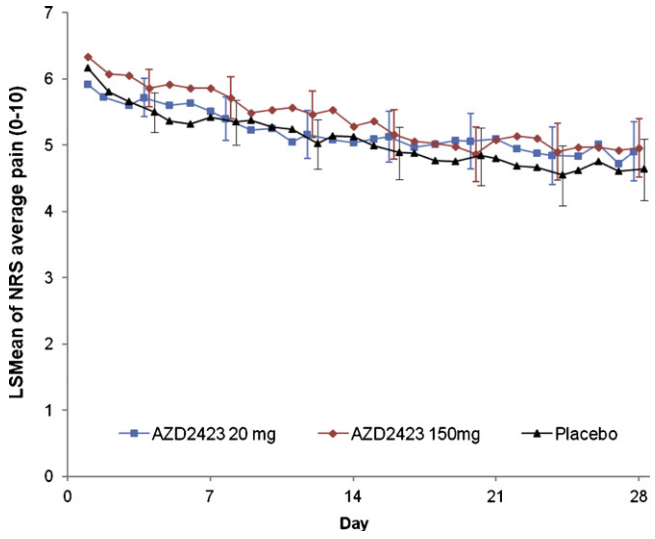

Fig. 3. Mean daily pain scores during treatment. LS means and 80% confidence intervals of daily NRS-average pain scores from treatment Day 1 to 28 in AZD2423 and placebo groups (mITT analysis set). Confidence intervals are shown every 4 days.

CCL2 plasma levels increased in a dose-dependent manner following treatment with AZD2423. The largest increase was seen during the first treatment week (Fig. 5). After that, CCL2 plasma levels reached a plateau. The CCL2 levels decreased from end of treatment, returning close to baseline values at the follow-up visit.

3.4. Pharmacokinetics

Median $C_{ss,av}$ was approximately 12 nmol/L (range 5.0–19 nmol/L) for AZD2423 20 mg and 110 nmol/L (range 60–187 nmol/L) for AZD2423 150 mg. Median $C_{ss,max}$ was approximately 24 nmol/L (range 9.9–48 nmol/L) for AZD2423 20 mg and 270 nmol/L (range 90–650 nmol/L) for AZD2423 150 mg.

3.5. Safety and tolerability

The overall frequency of AE was similar in the AZD2423 and placebo groups. A total of 53 patients experienced at least one AE in any category during the study: 15 patients (34%) in the AZD2423 20 mg group, 17 patients (36%) in the AZD2423 150 mg group and 21 patients (51%) in the placebo group. The most common AE in the AZD2423 groups were headache, dizziness, nausea and pyrexia, all in frequencies below 10%, not notably different from placebo. Three

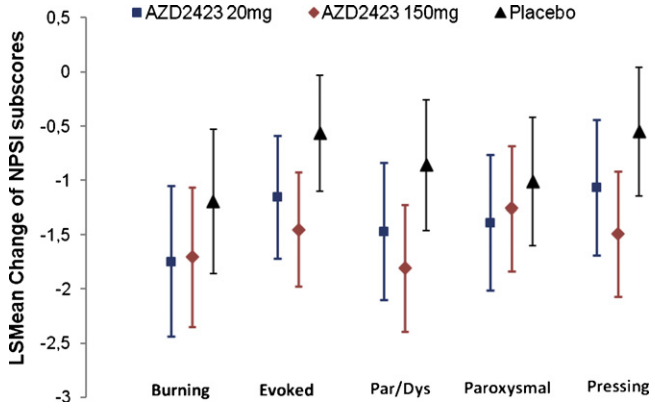

Fig. 4. Change in NPSI subscores from baseline to end of treatment. LS mean NPSI change and 80% confidence intervals from treatment Day 1 to 29 in AZD2423 and placebo groups (mITT analysis set).

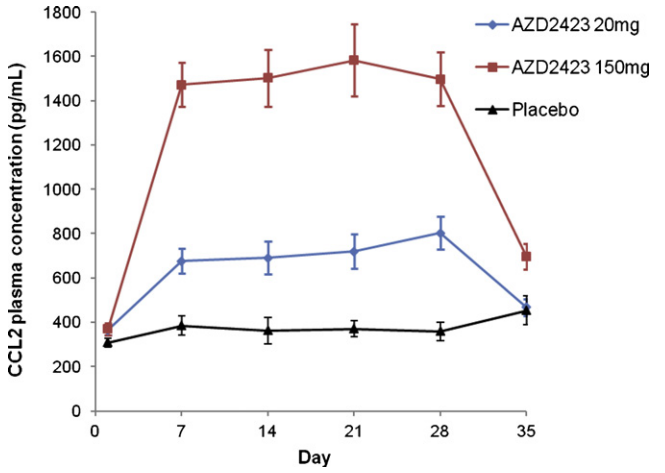

Fig. 5. CCL2 plasma levels over time. Mean CCL2 (±s.e.) plasma levels from treatment Day 1 to 35 (follow-up) for AZD2423 and placebo groups (safety analysis set).

patients in each treatment group (including placebo) discontinued treatment due to AE.

Four serious adverse events (SAE) were reported in three patients, all in the AZD2423 20 mg group. One patient who stopped dosing of his own accord after four days treatment had a myocardial infarction six days after stopping dosing. He recovered from this and was discharged from hospital after one week. However, one week after discharge from hospital the patient died due to sudden cardiac death. This patient had a known coronary artery disease and several cardiac risk factors. The investigator considered that the SAE and death were not causally related to study drug. Another patient with SAE was hospitalized due to asthmatic bronchitis (not causally related to study drug), from which he recovered. A third patient had diarrhea and urinary tract infection. He was treated with ciprofloxacin. The diarrhea became more severe and the patient was hospitalized and diagnosed with Clostridium difficile colitis, reported as an SAE. This SAE was judged by the investigator as causally related to study drug.

The only treatment-related change of laboratory parameters was a reduction of mean blood monocyte counts by 27% (from 0.45 to 0.33×10^9/L, SD = 0.12) in the AZD2423 150 mg group and by 9% in the 20 mg group. The monocyte counts were normalized at follow-up. There were no treatment-related changes of vital signs or ECG.

4. Discussion

The key finding of the present study was that AZD2423 20 mg or 150 mg did not differ from placebo with regard to the primary variable (change of the average pain intensity measured with NRS) in PDN patients. This finding was also supported by several secondary variables that did not show any difference between AZD2423 and placebo groups: response rates based on NRS average pain (≥30% and ≥50% pain reduction), NRS worst pain (≥30% and ≥50% pain reduction) and PGIC, as well as NRS pain interference on sleep or activities.

In contrast, the NPSI total score and subscores tended to be more reduced by AZD2423 than by placebo, in particular by the higher dose of AZD2423. Possibly, the NPSI results may indicate a response to certain sensory components of pain in patients with PDN, represented by the NPSI subscores of evoked pain, pressing/deep pain and paraesthesia/dysesthesia. However, these putative sensory effects were obviously not sufficient to influence the primary pain variable or the global and functional measures of pain.

The mean values of dynamic and static mechanical allodynia tended to decrease more in the AZD2423 groups than in the placebo group. However, the variability was high and the proportion of patients with allodynia was rather low, as would be expected in a population of PDN patients. With investigators experienced in sensory testing, high test–retest-reliability has been reported for examinations performed within two consecutive days [18]. This may be difficult to obtain in large multi-center trials where the experience of the investigators in sensory testing procedures varies.

There are several examples of failures to demonstrate efficacy in neuropathic pain clinical trials with new drug candidates [19]. Neuropathic pain of a certain etiology (e.g. diabetic polyneuropathy) can present with different sensory phenotypes, implying heterogeneity of pain mechanisms [20]. Therefore, it is conceivable that molecules with highly specific mechanisms of action which are not efficacious in the overall population, might still be efficacious in a subpopulation of patients. For new molecules, a better understanding is needed on how preclinical drug effects translate to potential drug effects in man [21], as well as understanding on how to define the appropriate study population in which to test a new molecular mechanism. The development of clinical tools for identifying certain pain mechanisms [17,20,22], and of explorative and adaptive clinical trial designs [23] might be ways forward.

AZD2423 had acceptable safety and tolerability. The overall AE rate and discontinuations due to AE did not differ between AZD2423 and placebo groups. One out of four SAE on AZD2423 20 mg was considered causally related. The patient had a Clostridium difficile infection diagnosed after treatment with ciprofloxacin. However, the investigator could not exclude that the study drug had contributed. Another patient with advanced cardiovascular disease died three weeks after having stopped treatment, in sudden cardiac death, which was not considered as causally related to study drug.

The monocytes were slightly reduced by AZD2423 and normalized after end of treatment. This has been described previously with an antibody against CCR2 [24]. Inhibition of transport of monocytes from the bone marrow to the blood has been suggested as a possible mechanism [25].

The achieved plasma levels of AZD2423 in the two dose groups were in line with predictions from pharmacokinetic data in healthy volunteers (unpublished data, AstraZeneca R&D). The plasma levels of the ligand CCL2 increased with increasing dose of AZD2423, also previously reported [24]. Possibly, the elimination of CCL2 is dependent on binding to the CCR2, and would be inhibited in the presence of CCR2-antagonist [24]. Both the observed reduction of monocytes and the elevation of CCL2 levels suggest that AZD2423 has interacted with the target CCR2.

In summary, the CCR2-antagonist AZD2423 showed no efficacy on NRS average pain scores and most of the secondary variables in an overall PDN population. The NPSI data suggested possible effects on certain sensory components of pain. The intended drug plasma levels were reached and biomarker data suggested that interaction with the target CCR2 had been attained. Therefore, it is concluded that this study provides evidence against an important analgesic effect of CCR2-antagonists in PDN.

Disclosure statement

J. Kalliomäki, B. Jonzon, K. Huizar, M. O'Malley, A. Andersson are employees of AstraZeneca R&D Södertälje, Sweden. D.M. Simpson has been consultant for NeurogesX, Pfizer, Allergan, Merz, Merck, Astellas, Ipsen, Forest, Acorda, Depomed, Syntaxin, Viromed, speaker for Eli Lilly, Merz, Astellas, US Worldmeds, and has received grant support from AstraZeneca, Pfizer, Allergan, Ipsen, Merz, US Worldmeds, Viromed.

Role of the funding source

The study was sponsored by AstraZeneca R&D. The authors are responsible for the study design, collection, analysis and interpretation of the data, and the decision to submit the paper for publication.

Conflict of interest statement

J. Kalliomäki, B. Jonzon, K. Huizar, M. O'Malley, A. Andersson are employees of AstraZeneca R&D Södertälje, Sweden. D.M. Simpson has been consultant for NeurogesX, Pfizer, Allergan, Merz, Merck, Astellas, Ipsen, Forest, Acorda, Depomed, Syntaxin, Viromed, speaker for Eli Lilly, Merz, Astellas, US Worldmeds, and has received grant support from AstraZeneca, Pfizer, Allergan, Ipsen, Merz, US Worldmeds, Viromed.

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Appendix A. List of site investigators "AZD2423 PDN study group"

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