

AstraZeneca	AZD2423
<b>Mechanism of Action</b>	Chemokine (C-C motif) receptor 2 (CCR2) antagonist <a href="http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=59">http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=59</a> <a href="http://www.ncbi.nlm.nih.gov/gene/729230">http://www.ncbi.nlm.nih.gov/gene/729230</a>
<b>Overview</b>	<p>AZD2423 is a potent orally bioavailable non-competitive, negative allosteric modulator of the CCR2 chemokine receptor. CCR2 is a receptor for monocyte chemoattractant protein MCP-1 (CCL2) and the closely related proteins MCP-2 (CCL8), MCP-3 (CCL7), and MCP-4 (CCL13). Human CCR2 exists as two forms, CCR2a and CCR2b, which differ at their C-termini by alternative splicing. Evidence obtained from studies on leukocytes suggests that MCP-1 binds preferentially to CCR2 and mediates monocyte chemotaxis. Studies have implicated MCP-1-mediated monocyte infiltration in pain and a range of inflammatory diseases. AZD2423 has been developed for the oral treatment of neuropathic pain and chronic obstructive pulmonary disease (COPD).</p> <p>In pre-clinical studies, AZD2423 inhibited MCP-1 induced calcium mobilization and chemotaxis of THP-1 cell line with an IC<sub>50</sub> of 4 nM. The AZD2423 affinity for CCR2 in human whole blood, measuring MCP-1 induced L-selectin shedding from monocytes, was the same. AZD2423 is highly selective (&gt; 500-fold) for CCR2. AZD2423 demonstrated robust analgesia in two rodent models of neuropathic pain and a pain model of joint destruction against heat, mechanical and weight-bearing endpoints. A significant (&gt; 500-fold) drop-off in potency was observed for several pre-clinical species (rat, mouse, dog, marmoset). Consequently several tool compounds have been used for most <i>in vivo</i> pharmacology studies; a tool CCR2 antagonist inhibited neuronal excitability in rat neuropathic models to heat, mechanical and electrical stimuli either via systemic administration or via administration directly to the spinal cord.</p>
<b>Safety/Tolerability</b>	<p>A comprehensive safety assessment package has been performed on AZD2423 including pivotal reproductive toxicity studies and general toxicity studies of 6 month duration in rat and dog. Identified target organs for toxicity are liver and cardiovascular function.</p> <p>In healthy volunteers, AZD2423 has been studied at single doses of up to 600 mg and in multiple ascending doses of up to 300 mg once daily for up to 14 days. Gastrointestinal side effects, (nausea and vomiting), determined a single dose MTD of 300 mg and multiple dose MTD of 150 mg. In patients (COPD and neuropathic pain) multiple doses up to 150 mg (pain) and 100 mg (COPD) for 28 days have been generally well tolerated.</p>
<b>Additional Information</b>	AZD2423 has been studied in several Phase 2a studies. Doses of up to 150 mg for 4 weeks have been tested examining its potential effects in pain and COPD. In the COPD study, treatment with AZD2423 (100 mg) was associated with a decrease in the number of monocytes in peripheral blood. This effect was observed within 1 week after start of treatment, was sustained over the 4-week treatment period, and is consistent with the mechanism of action, as was the observed increase in CCL2, the endogenous ligand.
<b>Suitable for and Exclusions</b>	<p>Reproductive toxicity studies support the inclusion of women of child-bearing potential in clinical studies, provided that pregnancy is prevented using a reliable form of contraception. Mycobacterium tuberculosis screening should be performed to exclude patients with latent tuberculosis until more information has been gained on the potential risk with CCR2-antagonists regarding host defense.</p> <p>Proposals for studies in COPD, ophthalmology or dermatology are not of interest.</p>
<b>Clinical Trials</b>	<a href="http://clinicaltrials.gov/ct2/results?term=AZD2423">http://clinicaltrials.gov/ct2/results?term=AZD2423</a>
<b>Publications</b>	None