AstraZeneca	AZD9056
Mechanism of Action	Purinergic receptor 2X, ligand-gated ion channel, 7 ($P2X_7$) antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=77&objectId=484 http://www.ncbi.nlm.nih.gov/gene/5027
Overview	AZD9056 is a potent, selective, orally bioavailable $P2X_7$ receptor antagonist. The $P2X_7$ receptor is an adenosine triphosphate (ATP)-gated cation channel expressed on a variety of cell types believed to play a role in inflammation. The P2X7 receptor is implicated in inflammatory disorders due to its presence in the affected tissues and its role in the maturation and release of the cytokines interleukin (IL)-1β and IL-18, which mediate inflammation and tissue destruction. AZD9056 has been developed for the treatment of inflammatory conditions such as rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD) and Crohn's disease. In pre-clinical studies, AZD9056 inhibited release of pro-inflammatory mediators from human peripheral monocytes (IL-1β and IL-18) and human alveolar macrophages (IL-1β) with IC_{50}'s of 10-13 nM and inhibited IL-1β release from human synovial cells isolated from RA joint tissue. AZD9056 demonstrated a high degree (> 1000-fold) of selectivity and specificity for the human P2X7 receptor compared to other P2X receptor subtypes and > 100-fold selectivity at other targets investigated with the exception of the non-specific sigma receptor (26-fold). AZD9056 has little affinity for P2X7 receptors in the mouse or rat, the species commonly used in models of inflammation. Treatment of rats with structural analogs of AZD9056 resulted in a significant reduction in disease severity in the streptococcal cell wall (SCW) model of arthritis, and a delay in the adjuvant-induced arthritis (AA) model.
Safety/Tolerability	A comprehensive safety assessment package has been performed on AZD9056 including pivotal reproductive toxicity studies and general toxicity studies of 6 month duration in rat and dog and 12 month duration in non-human primate. Identified target organs for toxicity are the cardiovascular system, liver and biliary tree, and upper gastrointestinal tract. Additionally, AZD9056 is considered to be a developmental toxicant (cleft palate abnormalities were observed in rats). AZD9056 (50-400 mg) was generally well tolerated in RA patients (receiving background methotrexate or sulphasalazine) when given for 6 months once daily. Gastrointestinal adverse events were the most commonly reported and were dose-related and mainly mild to moderate in nature.
Additional Information	AZD9056 has been studied in Phase 2 clinical trials in RA, COPD, and Crohn's disease patients. No treatment related changes comparing AZD9056 (50, 100, 200 and 400 mg UID for 6 months) to placebo or etanercept (50 mg once a week) were noted in RA patients receiving background methotrexate or sulphasalazine on the primary endpoint of ACR20. However, some separation from placebo was observed for the AZD9056 treatment groups in the total Sharp score, which was primarily evident in the erosion score. In patients with moderate to severe COPD no significant effects on lung function parameters were noted when comparing AZD90566 (400 mg UID for 4 weeks) with placebo and in a 4 week trial in patients with Osteoarthritis there was no significant effect on pain outcomes However, a statistically significant decrease in Crohn`s Disease Activity Index (CDAI) from baseline was noted in Crohn's patients receiving 200 mg AZD9056 (UID for 4 weeks).
Suitable for and Exclusions	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. Proposals for use in orphan indications would be particularly welcome. Studies in COPD, rheumatoid arthritis, ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD9056
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AZD9056