AstraZeneca	AZD1236
Mechanism of Action	Matrix metalloproteinase 9|12 (MMP9|MMP12) inhibitor http://www.ncbi.nlm.nih.gov/gene/4318; http://www.ncbi.nlm.nih.gov/gene/4321
Overview	AZD1236 is a potent orally bioavailable MMP 9 and 12 (MMP9|MMP12) inhibitor. Matrix metallopeptidases (also known as metallopeptidases) are a family of enzymes involved in the breakdown and regulation of extracellular matrix and the cleavage and release of cell surface proteins, they are also involved in the pathophysiology of a number of disease processes; for example MMP9 and MMP12 have been implicated in osteoarthritis, aortic abdominal aneurysm and coronary heart disease. AZD1236 has been developed for use in chronic obstructive pulmonary disease (COPD). In pre-clinical studies, AZD1236 reversibly inhibited isolated human MMP9 and MMP12 enzymatic activity with IC_{50}'s of 4.4 nM and 6.0 nM, respectively. There was an approximately 20- to 50-fold reduction of activity at the isolated rat, mouse and guinea pig MMP12 orthologs, with IC_{50}'s of 120 nM, 140 nM and 330 nM, respectively. Similar reductions in potency were seen for MMP9 activity in the rat and mouse; guinea pig was not tested. AZD1236 has not been studied in other species. In an acute model of lung injury induced by the instillation of human MMP12 into rat lungs, AZD1236, dosed orally, inhibited the subsequent hemorrhage and inflammatory response by 50% at 0.32 mk/kg. In an acute model of cigarette smoke induced lung injury in the mouse, AZD1236 inhibited macrophage infiltration into bronchiolar lavage fluid in a dose dependent manner and to baseline levels at the highest concentration tested (300 mg/kg).
Safety/Tolerability	Pre-clinical toxicology studies have been performed rodent and dog species for up to 6 and 12 months, respectively. In the rat there were dose dependent minimal diffuse eye lens opacities at 6 months. In the dog, fibrodysplasia was observed in the subcutis after 12 months dosing. Other target organs include the kidney, adrenal glands, and ovary. Reproductive toxicology studies have demonstrated a potential for teratogenic effects. AZD1236 has been studied in healthy volunteer subjects and COPD patients. In volunteers, AZD1236 was well tolerated when given in single doses from 2 mg to 1500 mg and in multiple doses of 15, 75 and 500 mg for periods of up to 13 days. AZD1236 was also well tolerated in COPD patients with moderate to severe disease when given at 75 mg BID for 6 weeks.
Additional Information	In a single Phase 2a study in patients with moderate to severe COPD, no significant effects on lung function parameters were noted when comparing AZD1236 (75 mg BID for 6 weeks) with placebo.
Suitable for and Exclusions	The reproductive toxicology package indicates that AZD1236 can induce fetal malformations, therefore, the inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk benefit and the use of appropriate contraception. There are currently no data to support use in pediatric populations. Due to the emerging safety profile, proposals should be for diseases that require short term dosing regimens or alternatively for diseases of severe unmet medical need where a case for tolerating potential adverse events can be made. Proposals for use in COPD, ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD1236
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AZD1236