AstraZeneca	AZD1981
Mechanism of Action	Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) antagonist (prostaglandin D2 [DP2] receptor antagonist) http://www.ncbi.nlm.nih.gov/gene/11251
Overview	AZD1981 is a potent (binding IC_{50} of 4 nM), fully reversible, functionally non-competitive antagonist of human CRTh2. It blocks agonist-induced human eosinophil CD11b expression, shape change (including in whole blood), and chemotaxis as well as basophil shape change and Th2-cell chemotaxis at IC_{50}s of 8.5–50 nM. Potency is similar across species, as is plasma protein binding (~97%). AZD1981 is a weak (10s of µM) inhibitor *in vitro* of CYP2C9, OATP1B1 and UGT1A1 as well as inducer of CYP3A4. These potential drug-drug interaction (DDI) effects appear to translate to *in vivo* at super-pharmacologic doses/exposures (see below).
Safety/Tolerability	AZD1981 has been administered orally in healthy volunteers (single oral dose up to 4,000 mg; multiple doses up to 2,000 mg twice daily [BID] for 2 wks), asthma or COPD patients (up to 100 mg, BID for 4 wks), and asthmatics (up to 400 mg BID for 12 wks). A small percentage of patients treated with AZD1981 had notable elevations of ALT and AST without notable increase in total bilirubin. Results suggest a dose-response relationship with the highest percentage of subjects having identified liver function test (LFT) abnormalities in the AZD1981 400 mg BID group (~2–3% above placebo). In all cases, transaminases returned to baseline after AZD1981 was stopped. However, the possibility that AZD1981 may be associated with an increased risk of liver injury cannot be excluded. In completed DDI studies, AZD1981 at 400 or 500 mg BID, but not at 100 mg BID, increased the plasma exposure of ethinyl estradiol in female volunteers receiving a combined oral contraceptive (COC), warfarin (CYP2C9 substrate) and pravastatin (OATP1B1 substrate), while decreasing midazolam (CYP3A4 substrate). Preclinical safety studies of up to 12 months duration have been performed.
Additional Information	Target engagement was demonstrated in the single ascending dose (SAD) and multiple ascending dose (MAD) Phase 1 studies using an *ex vivo* whole blood PGD_2-induced eosinophil shape change assay (A_2 = 35nM). Data from these as well as asthma efficacy studies indicate effective target coverage at doses of 40–80 mg BID or three times daily (TID).
Suitable for and Exclusions	Preclinical reproductive toxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Given the potential for DDI and LFT effects (see above), dosing regimen (level and duration) as well as inclusion/exclusion criteria should be selected carefully to support a favorable risk-benefit. There are currently no clinical data to support use in pediatric populations below 12 years of age, although existing preclinical data would support clinical studies in a pediatric population of > 5 years. Proposals for studies in dermatology indications are not of interest at this time.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=azd1981&Search=Search; http://www.astrazenecaclinicaltrials.com/Submission/View?id=1994
Additional Characteristics: CNS Penetrance/Pediatric Diseases	AZD1981 has low CNS penetration and, thus, is probably not suitable for a CNS indication. Pediatric disease proposals will be considered. However, due to the lack of prior experience in pediatric subjects, use will depend on risk/benefit, dosing duration and regimen, and age of the pediatric population.
Publications	http://www.ncbi.nlm.nih.gov/pubmed/?term=azd1981