

AstraZeneca	AZD9668
Mechanism of Action	Neutrophil elastase (NE) inhibitor http://www.ncbi.nlm.nih.gov/gene/1991
Overview	AZD9668 is a potent, selective and reversible inhibitor of human neutrophil elastase (IC ₅₀ at recombinant-, plasma- and cell- [including primed neutrophil] associated NE were 12, 44 and 50 nM, respectively). In a panel of 319 other selectivity assays there was no inhibition at concentrations < 3 μM. AZD9668 is ~36 to 44 times less potent at the rat, mouse and dog orthologues. <i>In vivo</i> , AZD9668 prevented acute lung injury (hemorrhage) induced by instillation of human NE with an ED ₅₀ of 0.85 mg/kg, orally (p.o.; estimated plasma concentration = 2.8 nM). In a 4-day cigarette smoke exposure model, AZD9668 dose-dependently reduced both neutrophil numbers and IL-1β levels in bronchoalveolar lavage fluid (maximal inhibitions of 45% and 78%, respectively, at 10 mg/kg, p.o.). AZD9668 is a P-glycoprotein (P-gp) substrate, not extensively metabolized or plasma protein bound, and primarily excreted via the feces.
Safety/Tolerability	AZD9668 has been administered orally to Caucasian and Japanese healthy volunteers in single doses up to 120 mg and multiple doses up to 70 mg twice daily (BID). In Phase 2 studies, AZD9668 (5, 20 and 60 mg, BID) were administered for 2, 4 or 12 weeks in patients with COPD, cystic fibrosis (CF) or bronchiectasis. Infrequent (1–3%) elevation in liver enzymes (ALT and/or AST) or bilirubin has been found in AZD9668 compared to placebo-treated subjects. To date, > 1000 patients have received AZD9668 at up to 60 mg BID for up to 12 weeks. Preclinical studies of up to 12-month duration have been performed.
Additional Information	In a Phase 1 healthy volunteer study, AZD9668 at doses ≥ 60 mg (equivalent to ~12 x IC ₅₀ in plasma) produced a > 90% inhibition of zymosan-stimulated neutrophil elastase activity in an <i>ex vivo</i> whole blood assay. In 28-day Ph2a studies at 60 mg BID, bronchiectasis and CF patients had significantly reduced sputum and plasma inflammatory biomarkers while bronchiectasis patients alone showed improvements in lung function (forced expiratory volume in 1 second [FEV ₁] and forced vital capacity [FVC]) and quality of life (SGRQ-C score). In follow-on 12-week Phase 2b studies, there was no significant treatment benefit in COPD patients also treated with tiotropium or budesonide/formoterol, neither were there effects of AZD9668 on lung function in patients with cystic fibrosis.
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. Due to elevations in liver enzymes noted in Phase 2 studies, liver function tests (LFTs) should be monitored and a careful risk/benefit assessment as well as exclusion criteria considered for any future clinical study. Suitable for study in indications, sub-populations and/or endpoints that are manifestly distinct from those previously studied for this compound or mechanism of action.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD9668 ; https://www.clinicaltrialsregister.eu/ctr-search/search?query=AZD9668
Additional Characteristics: CNS Penetration/Pediatric Diseases	AZD9668 has low CNS penetration and, thus, is probably not suitable for a CNS indication. Studies in pediatric populations for which there is no adult population will be considered. Studies for diseases/conditions that have a pediatric and adult population will also be considered if studies in a pediatric population are scientifically justified. However, due to the lack of juvenile toxicology data or 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=AZD9668