AstraZeneca	AZD3241
Mechanism of Action	Myeloperoxidase (MPO) inhibitor https://www.ncbi.nlm.nih.gov/gene/4353
Overview	AZD3241 is an orally absorbed, centrally penetrant, irreversible inhibitor of human MPO (IC_{50} 630 nM for enzyme; 88 nM for PMA stimulate neutrophils and zymosan stimulated whole blood). AZD3241 is 14x more potent for human MPO than thyroid peroxidase (TPO), but equipotent in inhibiting bovine lactoperoxidase (LPO). No significant interactions were observed for any other of the over 150 targets (receptors, enzymes, transporters, and ion channels) tested, resulting in a selectivity of more than 15- to 150-fold. AZD3241 efficiently inhibited MPO activity *in vivo* during acute peritonitis in rats and has consistently shown neuroprotective efficacy in MPTP-lesioned mice, a model of Parkinson's Disease (PD). In the proteolipid protein (PLP)-α-synuclein transgenic multiple system atrophy (MSA) mouse model, AZD3241 demonstrated significant neuroprotection at 180 µmol/kg BID orally (steady-state plasma ~3 µmol/L; > 0.5 µmol/L for ~50% of the time), with preservation of neurons at the level of substantia nigra pars compacta, striatum, cerebellar cortex, pontine nuclei, and inferior olivary complex, as well as functional recovery measured by four different behavioral tests (motor score, flex field, pole test, and stride length test).
Safety/Tolerability	To date, a total of ~250 subjects have received AZD3241 in seven clinical studies (four Phase 1 in heathy volunteers, two Phase 2a in PD subjects, and one Phase 2a in Multiple System Atrophy subjects). In the Phase 1 studies, multiple doses of up to 900 mg BID were safe and well tolerated. In the Phase 2a studies, 8 – 12 weeks of treatment with up to 600 mg BID was generally well tolerated. Headache was the most common adverse event leading to discontinuation. Preclinical studies of up 6 months in rats and 9 months in dogs have been performed, supporting chronic dosing.
Additional Information	AZD3241 significantly decreased plasma MPO activity in healthy and PD subjects at 600 mg BID. In a Phase 2a PET study in PD subjects, AZD3241 at 600 mg BID for 8 weeks reduced [^{11}C]PBR28 binding to the mitochondrial translocator protein (TSPO), a biomarker of microglia activation, compared to baseline and placebo across all brain regions, including nigrostriatal regions, thalamus, cerebellum, limbic cortex, and temporal cortex. These results support the hypothesis that inhibition of MPO has a beneficial effect on neuro-inflammation.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Based on *in vitro* experiments, the risk of drug-drug interactions is low.
Clinical Trials	https://clinicaltrials.gov/ct2/results?term=AZD3241&Search=Search
Additional Characteristics: CNS penetrance/ Pediatric Diseases	AZD3241 is CNS penetrant and, thus, potentially suitable for appropriate CNS indications. Pediatric disease projects cannot be supported at this time.
Publications	https://www.ncbi.nlm.nih.gov/pubmed/?term=AZD3241; https://www.ncbi.nlm.nih.gov/pubmed/22161470