AstraZeneca	AZD7268
Mechanism of Action	δ Opioid receptor agonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=317 http://www.ncbi.nlm.nih.gov/gene/4985
Overview	AZD7268 is a potent, selective, orally bioavailable and CNS penetrating δ opioid receptor agonist. There are 3 opioid receptor subtypes, μ-receptors, κ-receptors, and δ-receptors, which are implicated in nociceptive and emotional responses, albeit in qualitatively different manners. AZD7268 was originally developed for depression and anxiety disorders. In pre-clinical studies AZD7268 has an affinity (Ki) of 0.3nM for the recombinant human δ-Opioid receptor and increased [^{35}S]GTPγS binding with an EC_{50} of 12 nM. It is ~1000-fold selective for other opioid receptors. AZD7268 possesses anxiolytic activity in animal models, including the conflict test in rats (median effective dose (ED_{50} = 0.6 mg/kg) and novelty suppressed feeding test in mice (ED_{50} = 0.3mg/kg).
Safety/Tolerability	A comprehensive safety assessment package has been performed on AZD7268 including pivotal reproductive toxicity studies and general toxicity studies of 3 month duration in rat and dog. Identified targets for toxicity were effects on cardiovascular function. Single ascending dose studies have been carried out in volunteers at doses up to 40 mg in which syncope and hypotension/dizziness were considered dose limiting. Multiple doses in volunteers up to 30 mg BID were generally well tolerated, with changes of fasting serum glucose and AST and/or ALT being of undetermined clinical significance. In patients with major depressive disorder and co-morbid anxiety a dose of 15 mg bid was generally well tolerated.
Additional Information	AZD7268 has been studied at a dose of 15 mg BID for 28 days in patients with major depressive disorder and co-morbid anxiety. The primary and secondary efficacy endpoints were not met for the full analysis set (FAS) or pharmacokinetic compliant analysis set (PKCAS). However, some reductions in symptoms associated with depression were observed in exploratory analyses using a subset of patients with co-morbid anxiety (baseline HAM-A ≥ 16).
Suitable for and Exclusions	Reproductive toxicity studies identified a slight effect on fetal survival and a marked increase in major skeletal malformation at high dose. 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. No data are available as yet to support use in pediatrics. Proposals for studies in unselected populations of patients with major depressive disorder and/or anxiety as monotherapy, in ophthalmology, or in dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD7268
Publications	None