AstraZeneca	AZD0328
Mechanism of Action	Nicotinic acetylcholine receptor alpha 7 (α7 nAChR) agonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=468&familyId=76 http://www.ncbi.nlm.nih.gov/gene/1139
Overview	AZD0328 is a potent orally bioavailable α7 nAChR agonist. The α7 nAChR is a pentameric ion channel with widespread distribution in both the central and peripheral nervous systems where they are involved in normal physiology but also the pathophysiology of a number of conditions such as Alzheimer's disease, cognition and related deficits, stroke, myocardial infarction and sepsis. AZD0328 has been developed for use in patients with cognitive impairment such as Alzheimer's disease or Schizophrenia. In pre-clinical studies, AZD0328 displaced [^{3}H]α-bungarotoxin in HEK membranes expressing human α7 nAChRs with a Ki of between 3 and 4.7 nM and activated whole cell currents in Xenopus oocytes expressing human, rat or mouse α7 nAChRs with EC_{50}'s of 1.9, 1.1 and 1.0μM, respectively. It is equi-potent at the serotonin (5HT-3) receptor. AZD0328 is efficacious in a variety of *in vivo* models of learning and memory in mice, rats and primates. For example, in a rat model of operant conditioning, AZD0328 significantly increased the number of reinforcers earned when dosed either orally or subcutaneously (sc) between 14 and 46 μg/kg, while in rats with a bilateral fimbria-fornix lesion, which causes a severe disconnection of hippocampal signaling, those treated with 14 μmol/kg (sc) of AZD0328 showed a significant restoration of long term potentiation, relative to vehicle-lesion treated animals.
Safety/Tolerability	A comprehensive safety assessment package has been performed on AZD0328 including preclinical toxicity studies of 6 month duration in rat and dog and pivotal reproductive toxicity. Identified target organs for toxicity are the kidney and cardiovascular system. In healthy volunteers, single ascending dose (SAD) studies have been conducted at concentrations ranging from 0.001 to 2.0 mg and in multiple ascending dose (MAD) studies from 0.001 to 1.35 mg given once-daily for 13 days. In the SAD studies, the most common adverse event was nausea which was observed in 5 of 48 subjects at the highest doses studied. In the MAD study facial flushing and gastrointestinal disturbances were the most common adverse events attributable to AZD0328 and were dose related. The MTD for multiple administration in the context of the original indication was determined to be 1 mg. In a Phase 2a clinical trial, there appeared to be a dose-related incidence of nausea, although at the presumed optimal dose range this was approximately 5%.
Additional Information	AZD0328 has been studied in a single 14 day Phase 2a clinical trial in patients with schizophrenia, concurrently taking an additional anti-psychotic drug, with a primary outcome of improved cognition at doses ranging from 0.00093 to 0.675 mg. No statistically significant improvement in cognition, or other secondary endpoints, was observed.
Suitable for and Exclusions	The reproductive toxicology package indicates embryo lethality and increased implantation loss, 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. The emerging safety profile is consistent with supporting future studies that are in patients suffering from chronic diseases and which, subject to ratification, may last up to six months. AZD0328 is renally cleared and therefore future studies will require an assessment of the risk-benefit for subjects with renal impairment. Proposals for use in orphan indications would be particularly welcome; studies of cognitive deficit, ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD0328
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AZD0328