

AstraZeneca	AZD8529
Mechanism of Action	Metabotropic glutamate receptor 2 (mGluR2) positive allosteric modulator (PAM) http://www.ncbi.nlm.nih.gov/gene/2912
Overview	AZD8529 is a potent (binding K_i of 16 nM) and specific PAM for mGluR2. It potentiates the effects of glutamate on mGluR2 with an EC_{50} of 195 nM (max glutamate EC_{50} shift of 7.4-fold) and E_{max} of 110% (max potentiation of E_{max} by 1.3-fold). Specific activity as an agonist, antagonist or PAM was tested for recombinantly expressed mGluR1, 3, 4, 5, 7 and 8 in HEK cells. AZD8529 produced only weak PAM for mGluR5 (EC_{50} of 3.9 μ M) and antagonism for mGluR8 (IC_{50} of 23 μ M). Selectivity was evaluated at 10 μ M in 161 receptor, enzyme or ion channel assays with only modest activity found at 9 targets. AZD8529 exhibits concentration-dependent reductions in psychomotor activity and neural firing in rodent models. AZD8529 alone (57.8 to 115.7 mg/kg, sc) or in combination with an atypical antipsychotic (5.8 mg/kg, sc of AZD8529) reversed the hyper-locomotion induced by administration of phencyclidine in a murine model of schizophrenia.
Safety/Tolerability	AZD8529 has been administered at single doses of up to 310 mg and repeated doses up to 250 mg once daily for 15 days in healthy human volunteers. Adverse events noted were mild and included headache and gastrointestinal upsets. In patients with schizophrenia, AZD8529 has been administered at a dose of 40 mg every second day for 28 days. The most common adverse events were headache and dyspepsia. Preclinical studies of up to 3-month duration have been performed. After 1- and 3-month treatment in rats and 3-month treatment in dogs, reversible effects on testis were described. Additionally, cataracts were seen after 3 months treatment in the rat, and mild effects on liver and ovary are also reported at high dose.
Additional Information	In healthy volunteers, AZD8529 levels in the CSF (taken 6 hrs after the day 12 dose of 60 mg, every day [QD]) was approximately half the plasma free-fraction, suggesting good blood-brain barrier (BBB) penetration. In a 28-day Phase 2 study in schizophrenic patients administered 40 mg once daily, there was no change from placebo in the primary outcome measure of the Positive and Negative Syndrome Scale (PANSS) score.
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. The preclinical safety findings prompt the careful monitoring for effects on reproductive organs, eyes (slit lamp) and liver in future clinical studies of > 3 weeks duration. 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://www.clinicaltrials.gov/ct2/results?term=AZD8529&Search=Search
Additional Characteristics: CNS Penetrance/Pediatric Diseases	AZD8529 is a CNS penetrant (see above) and, thus, potentially is suitable for appropriate CNS indications. Pediatric disease projects cannot be supported at this time.
Publications	None yet