AstraZeneca	AZD5213
Mechanism of Action	Histamine receptor 3 (H_3) antagonist (inverse agonist) https://www.ncbi.nlm.nih.gov/gene/11255
Overview	AZD5213 is potent (Ki 0.5 nM; dissociation K_B 0.2 nM), competitive, rapidly reversible, functional antagonist (inverse agonist; IC_{50} of 3 nM) at the human H_3 receptor. It occupies H_3 receptors with an *in vivo* pKi of 8.5, 8.3 and 8.4 (free concentration in brain) for rat, mouse and NHP, respectively. AZD5213 was tested against a broad panel of 335 other receptors and enzymes at 10 µM without significant activity (>50% inhibition) for any. *In vivo*, it triggers the release of histamine as well as the neurotransmitters acetylcholine, dopamine and norepinephrine in rat prefrontal cortex following dosing or 0.33 mg/kg, po and increased tele-methylhistamine in the CSF of cynomolgus monkeys at 0.1 mg/kg, po. At similar dose levels, AZD5213 has been shown to reverse scopolamine-induced memory deficit, increase novel object recognition, and reverse neuropathic in various rodent models.
Safety/Tolerability	AZD5213 has been administered orally to 165 healthy volunteers in single doses up to 80 mg and multiple doses up to 18 mg QD for 10 days. The most frequent and dosing limiting adverse effects were sleep disorder, night sweats, and decreased quantity as well as quality of sleep. Other common AEs include mild to moderate nausea and headache. 61 subjects with mild Alzheimer's Disease or Cognitive Disorder were treated with AZD5213 at 0.5, 2, or 6 mg QD for up to 28 days and compared to 20 on placebo. Total sleep time was reduced in patients receiving 2 or 6 mg/day; however, measures of psychomotor function/speed of processing, visual attention/vigilance, and visual learning/memory were not significantly affected and treatment with AZD5213 did not affect subjective daytime sleepiness. 18 adolescent subjects (ages 12 – 17 years) with Tourette's Disorder received 0.5 or 2 mg AZD5213 for 28 days. Based on the clinical data generated to date, AZD5213 appears to have a relatively benign profile. Preclinical studies of up to 6 months duration have been performed.
Additional Information	AZD5213 was rapidly absorbed (T_{max} of 0.7 – 2.0 hrs.) after oral administration with an overall terminal $t_{½}$ of 5-7 hours. *In vitro* studies show a low risk for DDIs. PET studies demonstrated saturable, concentration-dependent occupancy of H_3 receptors with an estimated Ki, pl of 1.14nM. Receptor occupancy of ~50% was achieved at a dose of 0.1 mg.
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. Indications and dosing regimen should consider the potential for and optimisation of efficacy while minimizing the mechanism-based adverse effect on sleep. Given the strong association between dose, plasma concentration and brain receptor occupancy as well as the rapid absorption and relatively short $t_{½}$, data is available to potentially optimise benefit (day time efficacy) versus risk (night time sleep disturbance).
Clinical Trials	https://clinicaltrials.gov/ct2/results?term=azd5213&Search=Search
Additional Characteristics: CNS penetrance	AZD5213 is CNS penetrant (see above) and, thus, potentially suitable for appropriate CNS indications.
Publications	https://www.ncbi.nlm.nih.gov/pubmed/?term=azd5213