

AstraZeneca	AZD2624
Mechanism of Action	Neurokinin-3 receptor, tachykinin receptor 3 (NK3R; TACR3) antagonist http://www.ncbi.nlm.nih.gov/gene/6870
Overview	<p>AZD2624 is a potent human NK3R antagonist (K_i of 2 nM; calcium flux IC₅₀ of 2.6 nM) with >100-fold selectivity over a panel of 184 other receptors, enzymes and ion channels, including NK2R, NK1R and cholecystokinin 2 receptor (CCK2R). The major human metabolite has only slightly weaker human NK3R antagonist potency (calcium flux IC₅₀ of 9.0 nM) with selectivity of >10-fold to NK2R. In gerbils, AZD2624 significantly reversed senktide-induced suppression of locomotor activity by both the intraperitoneal and oral routes with ED₅₀ values of 0.48 mg/kg and 1.1 mg/kg, respectively.</p> <p>From consideration of <i>in vitro</i> data and <i>in vivo</i> findings in pre-clinical species, AZD2624 is anticipated to demonstrate low CNS exposure at therapeutic doses.</p>
Safety/Tolerability	<p>AZD2624 has been administered orally in single doses up to 80 mg and multiple doses up to 30 mg twice daily (BID) for 7 days or 40 mg every day (QD) for 6 days in healthy volunteers, and also at 40 mg QD for 28 days in schizophrenia patients. The most common AEs in excess of placebo were headache, abdominal discomfort, eye pain, somnolence and upper respiratory tract infection, all mild to moderate, as well as an apparent primary pharmacology, mechanism-based reduction in serum testosterone in males.</p> <p>Preclinical studies of up to 3 months duration have been performed.</p>
Additional Information	<p>Clinically significant, transient, reversible, and asymptomatic reductions in total serum testosterone have been noted at doses/exposures estimated for primary target engagement in male subjects. Testosterone and LH lowering have also been seen with other NK3R antagonists (talnetant [GlaxoSmithKline] and osanetant [Sanofi]; ref). NK3R antagonism-induced lowering of hypothalamic GnRH pulsatility is the suspected cause. The effect of AZD2624 on female gonadal hormones is not known.</p> <p>AZD2624 at 40 mg QD for 28 days was not found to be effective in schizophrenia patients.</p>
Suitable for and Exclusions	<p>Until further data are available, AZD2624 is considered not suitable for administration in pregnant or lactating women or in women who are trying to conceive. Conception while on treatment must be avoided. Since interaction with the metabolism of oral contraceptives cannot be excluded, trial protocol will require the use of alternative highly effective forms of contraception.</p> <p>Monitoring for reductions in total serum testosterone should be included in male patients.</p> <p>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.</p>
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD2624&Search=Search
Additional Characteristics: CNS Penetration/Pediatric Diseases	<p>AZD2624 has low CNS penetration and, thus, is probably not suitable for a CNS indication.</p> <p>Pediatric disease projects cannot be supported at this time.</p>
Publications	http://www.ncbi.nlm.nih.gov/pubmed/20937004