Pfizer Inc.	PF-03463275
Mechanism of Action	Glycine transporter 1 (GlyT1) inhibitor Solute carrier family 6 (neurotransmitter transporter, glycine), member 9 (SLC6A9) inhibitor http://www.ncbi.nlm.nih.gov/gene/6536
Overview	PF-03463275 is an orally bioavailable, centrally penetrant, potent (Ki = 13 nM), reversible, selective (GlyT2 Ki > 1 mM), competitive inhibitor of the human GlyT1 transporter.
Safety/Tolerability	PF-03462375 was generally safe and well tolerated for 7 days in doses up to 25 mg Q6h in healthy subjects and up to 25 mg Q8h in subjects with schizophrenia stabilized on a second generation anti-psychotic. The most frequently reported adverse events (AEs) in this population were headache, somnolence, dry mouth, insomnia, and pollakiuria. Sporadic increases in aspartate aminotransferase/alanine aminotransferase (AST/ALT) and glucose have been noted. Visual perception changes were noted at the highest doses tested. Non-clinical toxicology data support human studies up to 3 months in duration.
Additional Information	Target coverage in humans was demonstrated by increased CSF glycine levels. PF-03463275 may be a substrate for p-glycoprotein (P-gp)-mediated efflux. CYP2D6 and CYP3A are primarily responsible for the metabolism of PF-03463275. PF-03463275 administered as an immediate release formulation has a t½ of ~3-6 hours. It is also available as a controlled-release tablet. Oral administration to humans produces measurable concentrations in CSF over a 6 hour sampling period. No clinical efficacy.
Suitable for and Exclusions	Clinical studies in adult males and females of non-childbearing potential for up to 3 months in whom the potential benefit would justify potential risks. Subjects must be genotyped for CYP2D6 polymorphisms. Studies should be restricted to extensive metabolizers to minimize pharmacokinetic variability. Subjects must have ophthalmologic screening and be monitored for visual changes.
Clinical Trials	http://www.clinicaltrials.gov/search?term=%22PF-03463275%22
Publications	http://www.ncbi.nlm.nih.gov/pubmed/20186106