

Janssen (J&J)	JNJ-39393406
Mechanism of Action	Nicotinic acetylcholine receptor, $\alpha 7$ ($\alpha 7nAChR$) positive allosteric modulator http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=468&familyId=76 http://www.ncbi.nlm.nih.gov/gene/1139
Overview	JNJ-39393406 is a positive allosteric modulator at the nicotinic $\alpha 7$ receptor. <i>In vitro</i> , it potentiates a 100 μM choline-induced rise in intracellular calcium mediated by human $\alpha 7$ channels expressed in GH4C1 cells, with an EC_{50} of 660 nM (fluorimetric measurements). The concentration response curves of choline, acetylcholine and nicotine are shifted to the left (10-, 10- and 20-fold) and upwards (20-, 17- and 17-fold), indicating that JNJ-39393406 increases both the potency and efficacy of these agonists. The compound is selective for the $\alpha 7$ receptor and does not act on $\alpha 4\beta 2$, $\alpha 3\beta 4$ or 5-HT3A channels, and it does not act on $\alpha 4\beta 2$, $\alpha 3\beta 4$ or 5 HT3A channels, and it does not interact with a panel of 62 receptors and enzymes. JNJ-39393406 has shown bell-shaped dose-response activity in two out-sourced animal models: the auditory evoked potential (AEP) in DBA2 mice (0.63–5 mg/kg s.c., lower and higher doses were inactive), a model for sensory gating and the attentional set-shifting in rat (1.2 and 5 mg/kg s.c., partial effect at 0.3 mg/kg, not tested at doses higher than 5 mg/kg).
Safety/Tolerability	<p>Good Laboratory Practice toxicological studies were conducted in rat and dog up to 3 months dosing. In standard tests to assess genotoxicity, embryo-fetal safety, phototoxicity and skin sensitization potential, JNJ-39393406 was shown to be well tolerated. Main targets in the rat were the liver (mostly hepatocellular changes, basophilic hepatocellular foci), the coagulation system, red and white blood cells, and thyroid (hypertrophy, considered of low relevance to humans). Liver toxicity (hepatocellular foci, bile duct and oval cell proliferation, cholangitis, chronic inflammation after 3 months dosing and a 2-month dose-free period) and changes related to lymphocytes and reticulocytes were not reversible. The mechanism of the liver toxicity is being investigated, but so far the relevance to man has not been elucidated. In the dog, sinus tachycardia and minimally adverse effects on body weight, cholesterol and thrombocytes were observed and proved to be reversible. JNJ-39393406 was classified as a very mild eye irritant.</p> <p>During the single and multiple ascending-dose studies, no serious adverse events were reported and all adverse events were mild or moderate in severity. Most adverse events were considered not related or of doubtful relationship to the study drug by the investigator.</p> <p>In phase 1 clinical trials of JNJ-39393406, using doses from 3 mg to 800 mg in studies up to approximately 2 weeks, no significant safety signals were observed with good oral bioavailability when dosed orally as a nanosuspension. Exposure in plasma and CSF well exceeded levels applied in preclinical testing.</p>
Additional Information	In a multicenter, double-blind (DB), placebo-controlled (PC), randomized, four-way cross-over proof-of-mechanism study, JNJ-39393406 was tested in 39 regularly smoking male patients with schizophrenia in a set of electrophysiology measures. No indication was found that JNJ-39393406 has the potential to reverse basic deficits of information processing in schizophrenia (sensory P50 gating) or have a significant effect on other tested electrophysiological markers (MMN, P300 and quantitative resting EEG). Sensitivity analyses including severity of disease, baseline P50 gating, medication and gene variants of the CHRNA7 gene did not reveal any subgroups with consistent significant effects. CSF levels of the compound were measured in a separate trial and considered adequate. As mentioned above, this study only was testing regularly smoking male patients

	<p>with stable schizophrenia. Other populations or detailed cognitive measures were not tested.</p> <p>Independent of the primary pharmacology, JNJ-39393406 was tested in a series of inflammatory challenge models and exhibited anti-inflammatory properties. JNJ-39393406 exhibited anti-inflammatory properties at all of the tested doses in the thioglycollate-induced monocyte infiltration, lipopolysaccharide (LPS)-induced pulmonary inflammation, and ovalbumin-induced <i>in vivo</i> antibody production assays. In all of these assays, the maximal effect was achieved with the lowest dose of the compound, and no further dose escalation afforded any additional anti-inflammatory benefit. No statistically significant effect of the treatment was seen in the dextran sodium sulfate (DSS)-induced colitis model, while treatment with the reference compound Cyclosporine A yielded the expected protection in this model.</p>
Suitable for and Exclusions	<p>Studies of symptomatic treatment of Alzheimer’s disease and cognitive impairment in schizophrenia should be excluded.</p> <p>Current toxicology package supports human adult studies of up to 3 weeks duration.</p> <p>May be suitable for pediatric conditions, including neurodevelopmental and neurodegenerative disorders.</p>
Clinical Trials	<p>http://clinicaltrials.gov/ct2/results?term=JNJ-39393406</p>
Additional Characteristics: CNS Penetration/Pediatric Diseases	<p>Based on results of a DB, PC, single-dose, PK study in healthy subjects, under equilibrium conditions, CSF concentration is expected to be similar to unbound plasma concentration. CSF/plasma unbound ratio is approximately 0.45; therefore, brain penetration of JNJ-39393406 is good.</p> <p>This drug is amenable to exploration/use in pediatric populations provided necessary juvenile toxicology work is completed. Adult safety data supports use in pediatric populations. The relative bioavailability of the capsule versus solution formulations are 41% and 72%, respectively for C_{max} and AUC_{∞}. Solution/suspension formulations would be possible.</p> <p>Studies in pediatric populations for which there is no adult population will be considered. Studies for diseases/conditions that have a pediatric and adult population will also be considered if studies in a pediatric population are scientifically justified.</p>
Publications	<p>http://www.ncbi.nlm.nih.gov/pubmed/22766391</p>