Janssen Research & Development, LLC	JNJ-39269646
Mechanism of Action	Fast dissociating D2/D3/5-HT6 antagonist https://www.ncbi.nlm.nih.gov/gene/1813 https://www.ncbi.nlm.nih.gov/gene/1814 https://www.ncbi.nlm.nih.gov/gene/3362
Overview	Preclinical *in vitro* and *in vivo* studies profiled JNJ-39269646 as a mixed dopamine D2 and D3 antagonist with additional serotonin-6 (5-HT6) receptor affinity. JNJ-39269646 is active in classical animal models for antipsychotic activity (inhibition/normalization of stimulant-induced behaviors in rodents and conditioned avoidance responding in rats). JNJ-39269646 reverses phencyclidine-induced impairments in attention set shifting and increases new synapse formation in the hippocampus. JNJ-39269646 has minimal interaction with receptors associated with side effects (e.g. adrenergic alpha1, histamine H1, 5-HT2C, muscarinic).
Safety/Tolerability	Repeat dose Good Laboratory Practice toxicology studies in rat and dog up to 3 months support the administration of JNJ-39269646 to human subjects. The toxicity profile of JNJ-39269646 is overall commensurate with that of a dopamine D2 antagonist, characterized by hyperprolactinemia-induced tissue changes and decreases in generally activity. Additionally, phospholipidosis-related tissue changes were observed in rats. Embryofetal development studies, completed in rats and rabbits, support the inclusion of women of childbearing potential in clinical studies provided adequate measures are taken to prevent pregnancy and subjects have a negative pregnancy test at baseline. Overall JNJ-39269646 is safe and tolerated when administered to healthy subjects but, at high doses, JNJ-39269646 may induce restlessness and dystonia leading to treatment discontinuation, in addition, JNJ-39269646 transiently increases prolactin levels.
Additional Information	In clinic, after oral dose administration of JNJ-39269646, a concentration-related increase in striatal dopamine D2 occupancy was measured using 11C-raclopride PET (maximally 82% following 100 mg JNJ-39269646 administered twice daily bid]).Modeling of the concentration-response relationship suggests that JNJ-39269646 doses between 75 and 125 mg bid may have efficacy in the treatment of the acute phase of schizophrenia. The major CYP isoform involved in the metabolic clearance of JNJ-39269646 is CYP1A2. At clinically relevant doses, Cmax and AUC may increase 2- and 5-fold, respectively when co-administered with a potent CYP1A2 inhibitor (e.g., fluvoxamine).
Suitable for and Exclusions	Suitable for studies in schizophrenia (all phases) and bipolar disorder. Not suitable for pediatric study.
Clinical Trials	In 4 completed Phase 1 studies, 60 subjects received JNJ-39269646 once up to 400 mg and 63 at least twice up to 250 mg/day for 7 days.
Publications	None