

Pfizer Inc.	PF-03654746
Mechanism of Action	Histamine receptor 3 (H3) antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=33&objectId=264 http://www.ncbi.nlm.nih.gov/gene/11255
Overview	PF-03654746 is a potent (Ki = 2.3 nM), selective (> 1000x over H ₁ , H ₂ , H ₄ , hERG, and a panel of other receptors, ion channels, transporters, or enzymes), inverse agonist (functional antagonist) of the human H ₃ receptor. Binding and functional activity are 16- and 5-fold, respectively, lower for the rat receptor. PF-03654746 elevates extracellular levels of histamine and acetylcholine in the prefrontal cortex of conscious rats, as well as theta oscillation in anesthetized rats. It was also found to decrease wake time as well as increase NREM and REM sleep time in rats.
Safety/Tolerability	The primary dose limiting adverse events in clinical studies were persistent insomnia, sleep disturbances, parasomnias, and headache. Additional CNS, gastrointestinal, musculoskeletal, liver, and ECG abnormalities were noted less frequently, but should also be monitored in any future studies. Nonclinical toxicology data support clinical studies up to 3 months in duration.
Additional Information	PF-03654746 has failed to show efficacy superior to standard of care in clinical studies of Excessive Daytime Sleepiness associated with Narcolepsy (EDS), Cognitive Impairment in Schizophrenia (CIAS) and Alzheimer's Disease (AD), Attention Deficit Hyperactivity Disorder (ADHD), and Allergic Rhinitis (AR). Central H ₃ receptor occupancy was high, ranging from 31% to 94%, across the dose range of 0.1 mg to 4 mg.
Suitable for and Exclusions	A top human dose of 2 mg QD for up to 3 months with monitoring consistent with the toleration profile mentioned above.
Clinical Trials	http://www.clinicaltrials.gov/search?term=%22PF-03654746%22
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=PF-03654746