Pfizer	PF-03654746/H3 Receptor Antagonist
Mechanism of Action	Histamine Receptor 3 (H3) Antagonist IUPHAR link for target: http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=264&familyId=33 NCBI Gene data: http://www.ncbi.nlm.nih.gov/gene/11255
Overview	PF-03654746 is a potent (K_i = 2.3 nM), selective (>1000x over H1, H2, H4, hERG, and a panel of other receptors, ion channels, transporters, or enzymes), inverse agonist (functional antagonist) of the human H3 receptor. The radioligand binding assays compound's affinity at the rat receptor is 16-fold lower than at the human receptor. In functional assays measuring the ability of the compound to inhibit cAMP accumulation, the difference in potency shrinks to 5-fold. PF-03654746 elevates extracellular levels of histamine and acetylcholine in the prefrontal cortex of conscious, as well as theta oscillation in anesthetized, rats. It was also found to decrease wakefulness 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, GI, 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 in adults of 2 mg every day for up to 3 months with monitoring is consistent with the tolerability profile mentioned above. Amenable for exploration in all pediatric diseases
Clinical Trials	http://www.clinicaltrials.gov/search?term=%22PF-03654746%22
Additional Characteristics: CNS Penetrance/ Pediatric Diseases	CNS Penetrant 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.
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=PF-03654746