

SANOFI	SAR110894
Mechanism of Action	<p>SAR110894 (difumarate monohydrate) is a non-imidazole histamine H3 receptor (H3R) antagonist.</p> <p>IUPHAR link (target): <a href="http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=264&amp;familyId=33">http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=264&amp;familyId=33</a></p> <p>NCBI link (gene): <a href="http://www.ncbi.nlm.nih.gov/gene/11255">http://www.ncbi.nlm.nih.gov/gene/11255</a></p> <p>Other link (gene/protein information): <a href="http://www.hmdb.ca/proteins/HMDBP02715">http://www.hmdb.ca/proteins/HMDBP02715</a></p>
Overview	<p>SAR110894 is a selective and potent H3R antagonist, blocking auto and heteroreceptors located pre- and postsynaptically in the CNS. SAR110894 demonstrated pro-cognitive, attention and waking effect in rodents after acute and repeated administrations due to its ability to release histamine and acetylcholine in main regions of the brain controlling cognition and vigilance states. In rodent, additive pro-cognitive properties were observed after acute administration with the acetylcholinesterase inhibitor donepezil. In a Phase 2 trial, 290 Alzheimer’s disease (AD) patients at mild to moderate stage (MMSE 15-25) were treated in adjunct to donepezil, for 24 weeks (78, 72, 71, and 69 patients in placebo, 0.5 mg, 2 mg, and 5 mg, respectively). This study did not demonstrate a clinically or statistically significant difference in the primary efficacy endpoint (change from baseline to Week 24 in ADAS-Cog 11-item standard total score assessing cognitive function) between any of the active treatment groups and placebo group. The analyses of the key secondary endpoints were consistent with primary efficacy findings, with the exception of ADCS-ADL (functional measure), for which a statistically significant difference in favor of SAR110894 was observed for the change from baseline to Week 24 between the SAR110894D 5 mg group and placebo.</p>
Safety/Tolerability	<p>Teratogenicity, fertility affected in male and female and the propensity to induce cataracts in the rat are the main toxicological findings to consider for a clinical development.</p> <p>During Phase 1, safety and tolerability profile of SAR110894 was considered satisfactory in adult and elderly volunteers. The compound was tested up to 300 mg in single-dose studies and up to 30 mg in repeated (21 days) dose studies. Main events to note after single and repeated administrations were dose- and time-dependent sleep disturbances consisting of short awakenings during the night and enabling the demonstration of a central activity in humans. The mean terminal half-life ranged from 12 to 15 days after single or repeated oral doses.</p> <p>During Phase 2, treatment-emergent insomnias, muscle spasms, and depressed mood disorders and disturbances were more frequently reported in the SAR110894D 5 mg treatment group versus placebo. A slight signal was detected in lens opacity data in patients treated with 5 mg of SAR110894D compared to placebo, although the clinical significance of the findings cannot be determined at this stage.</p>

Additional Information	Additional properties have been discovered during Phase 2 trial in AD. In a transgenic mouse model of tauopathy, SAR110894 is endowed with disease-modifying properties as suggested by the prevention of TAU protein phosphorylation, neurofibrillary tangles formation in the cortex and hippocampus, and cognition improvement after a 6-month treatment. In the same model, SAR110894 reduced neuroinflammation (MIP-1 $\alpha$ ). Development of SAR110894 was stopped in AD due to its lack of efficacy on the primary endpoint (cognition) at 6 months.
Suitable for and Exclusions	SAR110894 is suitable for acute and long-term indications. Studies with a duration of > 6 months could be considered pending discussions with authorities. For instance, long trial in AD (disease modification) might be proposed. Exclude women of childbearing age, children, and adolescents due to teratogenicity and potential risk on reproductive organs development.
Clinical Trials	<a href="http://clinicaltrials.gov/ct2/show/NCT01266525?term=SAR110894&amp;rank=1">http://clinicaltrials.gov/ct2/show/NCT01266525?term=SAR110894&amp;rank=1</a>
Additional Characteristics: CNS Penetrance/Pediatric Diseases	SAR110894 is not suitable for pediatric indications. SAR110894 has proven CNS penetrance due to its ability to induce awakenings.
Publications	<a href="http://www.ncbi.nlm.nih.gov/pubmed/?term=SAR110894">http://www.ncbi.nlm.nih.gov/pubmed/?term=SAR110894</a>