

SANOFI	SAR152954
Mechanism of Action	<p>SAR152954 is a non-imidazole histamine H3 receptor (H3R) antagonist.</p> <p>IUPHAR link (target): http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=264&familyId=33</p> <p>NCBI link (gene): http://www.ncbi.nlm.nih.gov/gene/11255</p> <p>Other link (gene/protein information): http://www.hmdb.ca/proteins/HMDBP02715</p>
Overview	<p>SAR152954 is a selective and potent H3R antagonist, blocking auto and heteroreceptors located pre- and postsynaptically in the CNS. In rodents SAR152954 demonstrated pro-cognitive (0.01-1 mg/kg) and waking effects (at 10 mg/kg) due to its ability to release histamine and acetylcholine in brain regions controlling cognition and vigilance states. Receptor occupancy was seen in baboon at very low exposure. It is anticipated that compound has potential for a very large therapeutic window.</p>
Safety/Tolerability	<p>No major issues are anticipated for the compound based on preclinical toxicology and pharmacokinetic studies. In rodent models, this compound is rapidly absorbed orally ($t_{max} < 1$ h, half-life $< 1-4$ h) and distributed both systemically and centrally. It demonstrated an excellent preliminary safety profile based on standard non-clinical safety programs (drug-drug interaction, genotoxicity, and embryotoxicity).</p> <p>A Phase 1 evaluation on oral administration of this compound (single doses: 1, 3, 10, 20, 40, and 70 mg) was performed in a total of 48 fasting healthy male subjects. Compound is rapidly absorbed with acceptable clearance profile ($t_{max} \sim 2$ h, half-life ~ 17 h). There was no major safety issue encountered during Phase 1 study. The most common adverse event was spontaneously resolvable insomnia (from the dose of 10 mg).</p>
Additional Information	<p>Development of SAR152954 was stopped in Phase 1 for strategic reasons.</p>
Suitable for and Exclusions	<p>SAR152954 is suitable for acute/short-term indications (up to 1 month according to rat and dog tox studies available). Safety and tolerability profile after repeated administration in human healthy subjects has not been assessed.</p>
Clinical Trials	N/A
Additional Characteristics:	<p>SAR152954 is not “ready to use” for pediatric indications, but there is to date no major objection envisaging</p>

CNS Penetrance/Pediatric Diseases

a pediatric program. Of-note: safety studies necessary to support SAR152954's use in children under the age of 17 years have not been performed, specifically a "juvenile toxicity study" and a "pre/postnatal development toxicity study". 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.

SAR152954 has proven CNS penetrance (PET data available — reporting of insomnias after single administration in volunteers).

Publications

N/A