

SANOFI	SAR114137
Mechanism of Action	<p>SAR114137 is a novel, orally bioavailable (peripheral and central nervous systems) inhibitor of cysteine cathepsin S that has been developed for use in chronic pain.</p> <p>IUPHAR data for the target: http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2353</p> <p>NCBI Gene data for the gene: http://www.ncbi.nlm.nih.gov/gene/1520</p>
Overview	<p>SAR114137 is a potent inhibitor of human cathepsin S (K_i: 6 nM) and is 3- to 4-fold less active against cathepsin K (K_i: 16 nM). Cathepsin S inhibition was confirmed <i>in vivo</i> as oral administration of SAR114137 to mice inhibited the cathepsin S-dependent processing of MHCII in spleen. Shows analgesic-like properties in chronic pain models induced by inflammation/cartilage degradation or by nerve injury. Robust pain lowering efficacy in range <1 µg to <1 mg/kg in mouse with efficacy seen at 1 mg/kg in all tested species. Has a rapid onset of action in pain models (1-2 h) and a long duration of action (i.e., 3 days after last admin.) but no PK/PD relationship (short half-life). It is active in a wide range from (1, 10 mg/kg) and shows no anti-inflammatory activity.</p>
Safety/Tolerability	<p>SAR114137 was active in a variety of models of inflammatory/joint pain or neuropathic pain with efficacy seen at 1 mg/kg in all species (mouse, hamster, and guinea pig). Anti-inflammatory activity was not identified with doses up to 30 mg/kg in a CIA arthritis model. The main risk identified in preclinical toxicology studies was QT prolongation (reversible) observed at high exposures in dogs. A maximum tolerated dose of 3 mg was defined in Phase 1 studies owing to side effects (mainly dizziness). In a Phase 1 repeated dose study in elderly female subjects, a trend for a small QT prolongation was observed, however, with high variability.</p>
Additional Information	<p>Studies to date have only been conducted in healthy volunteers (young and elderly) to characterize pharmacokinetics (PK) following single and multiple administrations. To date, one combined four-subpart Phase 1 study with escalating single (1,2,3, and 5 mg) and repeated (0.5, 1, and 2 mg for 14 days) doses evaluated the safety, tolerability and PK of SAR114137, as well as a preliminary investigation of a potential food effect (0.5 mg) on the PK of SAR114137. The compound has not been evaluated to date in a disease population. An IND has not yet been submitted to FDA.</p>
Suitable for and Exclusions	<p>The properties and studies to date for SAR114137 are supportive for potential applications in acute pain. Reproductive and developmental toxicity data have not shown teratogenic effects. Evidence is sufficient to administer to post-menopausal women, women of childbearing potential using effective contraception. Evidence</p>

	is lacking on safety during pregnancy or breastfeeding. Safety has not been established for pediatric use.
Clinical Trials	Not available
Additional Characteristics: CNS Penetration/Pediatric Diseases	<p>SAR114137 is not suitable for pediatric studies.</p> <p>A specific brain penetration study has not been done. In the central nervous system studies, single doses of SAR114137 up to 2,000 mg/kg in rats had no behavioral effects over 24 hours, although body weight was decreased at doses ≥ 750 mg/kg. A depressant effect (decreased locomotor and rearing activities) was observed at 2,000 mg/kg during the dark/active phase of rats between 12.5 and 24.5 hours post dosing. Tissue distribution of total radioactivity, as determined by whole body autoradiography, was extensive after a single oral (50 mg/kg) and intravenous (i.v.; 10 mg/kg) dose of [14C]-SAR114137 to male Long Evans rats. After both i.v. and oral administration, concentrations of radioactivity in most tissues including central nervous system (brain and spinal cord) (brain/plasma ratio: SAR114137: 0.065-0.087 [mouse]; 0.067 [rat]) and reproductive system (testes and seminal vesicles) were comparable to or lower than in the blood. Following oral administration, the highest levels of radioactivity were observed in urine, bile, liver, kidney, and lung. Radioactivity was observed on the surface of lens and on the surface of joints. At 24 h, myocardium to blood total radioactivity ratio was 1.43. Radioactivity was observed in melanin-containing tissues (uveal tract and skin) with concentration comparable to that in blood. By 72 h post oral dose, concentrations of radioactivity in most tissues were close to background. By 2 weeks post oral dose, uveal tract, liver, and kidney were the only tissues with detectable radioactivity. Based on the data above [radioactivity in most tissues including central nervous system (brain and spinal cord)], it may be reasonable assume that it “may be” CNS-penetrant.</p>
Publications	http://www.sciencedirect.com/science/article/pii/S0939641113003093