Sanofi	SAR115740
Mechanism of Action	Transient receptor potential cation channel vanilloid 1 (TRPV1) antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=78&objectId=507 http://www.ncbi.nlm.nih.gov/gene/7442
Overview	SAR115740 is a novel, potent and selective transient receptor potential vanilloid 1 (TRPV1) antagonist which has been developed for chronic neuropathic and inflammatory pain. SAR115740 inhibited rat dorsal root ganglion capsaicin-induced currents with an IC_{50} of 1.21 nM and CHO cells stably expressing human TRPV1 with an IC_{50} of 3.82 nM. There was > 10-fold selectivity over related TRP channels (e.g., TRPM8, TRPV4) and no affinity (inhibition < 50% at 10 µM) for about 100 targets, including pain-related targets (CB2, COX1, COX2). Efficacy seen in many models of neuropathic (ED_{50} = 0.6 to 30 mg/kg) and inflammatory pain (MED = 2.8 and 30 mg/kg) in rodents.
Safety/Tolerability	Capsaicin-like, TRPV1 agonistic side-effects (e.g., transient hypothermia, urgency to urinate, hypersensitivity to touch) were seen in the 3-month dog and 6-month rat studies, suggesting a role for an agonist metabolite, SAR160024. However, histopathology including brain, spinal cord, sciatic nerve, and neurons of several organs and tissues did not substantiate those symptoms. SAR115740 absorbs UV light and was positive for photo-toxicity in an *in vitro* assay. SAR115740 may be a mechanism-based inhibitor and inducer of CYP3A4 and is likely an inhibitor of other CYPs (e.g., CYP2C8, 2C9, 1A2, 2B6, 2C19 and 2D6). SAR160024 also has the potential to be a mechanism-based inhibitor of CYP3A4.
Additional Information	Studies conducted to date have been in healthy volunteers only. SAR115740 has a half-life of > 3 days in man and a persistent major metabolite, SAR160024, TRPV1 agonist (EC_{50} = 156 nM), which was identified in the dog, which needs safety, ADME & discovery characterization. The half-life of SAR160024 was estimated at about 8 days, and it may cause hypothermia.
Suitable for and Exclusions	The combination of complex pharmacology and ADME profile results in high development and regulatory risks for the indication of chronic pain.
Clinical Trials	Studies conducted to date have been in healthy volunteers only.
Publications	None