Sanofi	SSR150106
Mechanism of Action	Chemokine receptor antagonist (TNFα release)
Overview	SSR150106 is a very potent, non-peptidic, orally active inhibitor of the synthesis of pro-inflammatory cytokines (mainly TNF-α) and various chemokines (mainly MCP-1). SSR150106 was investigated for the treatment of rheumatoid arthritis. SSR150106 administered by oral route inhibited TNF-α, IFN-γ, MCP-1, MIP-1α and MIP-1β production, and doses inhibiting 50% of their synthesis were in the range of 3-31 µg/kg. Metabolism studies indicated the main metabolite is an N-oxide (SSR150655), exhibiting similar activity. SSR150106 and its metabolite, SSR150655 have high affinity (in the nM range) for several central receptors as adrenergic, histaminic H1 and serotonergic 5HT1.
Safety/Tolerability	SSR150106, and its metabolite, are potent inhibitors of hERG (IC_{50} = 16 ng/ml and 64 ng/ml, respectively). In clinical studies ALT elevations of up to 12-fold upper limit of normal (ULN) have been observed. The most frequent treatment related adverse effects were nausea, vomiting, dizziness and headache.
Additional Information	In two clinical trials (in extensive CYP2D6 metabolizers only), SSR150106 had neither an effect on acute dental pain (120 µg, single dose), nor on C-reactive protein (CRP) in rheumatoid arthritis (RA) patients (ACT5488, 4 week treatment with 90 µg daily or every second day). The effect on RA signs and symptoms including chronic pain was weak compared to anti-TNFα biologics.
Suitable for and Exclusions	SSR150106 is almost exclusively metabolized via CYP2D6 to the active metabolite, which is the main circulating compound. This is confirmed by the significantly higher exposure of parent compound in poor metabolizers (PM) by a factor of 25-30 (C_{max}) and 50-60 (AUC) as compared to extensive CYP2D6 metabolizers (EM). No dose/dosing regimen that can be used for both EM and PM could be identified, limiting further development of SSR150106 to the EM population. While doses of 90 µg were used in ACT5488 in EM patients, SSR150106 exposure (AUC) from 30 µg in PM already exceeds by 7-fold the AUC of NOEL in dogs (0.01 mg/kg/day).
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=SSR150106
Publications	None