Sanofi	AVE5530 (canosimibe)
Mechanism of Action	Acyl-coenzyme A:cholesterol *O*-acyltransferase (ACAT) inhibitor Cholesterol absorption inhibitor http://www.ncbi.nlm.nih.gov/gene/38
Overview	Pre-systemic inhibition of intestinal cholesterol absorption. Poorly absorbed (< 3%) in contrast to ezetimibe, which is absorbed from the gastrointestinal (GI) tract. Minimally absorbed from GI tract: very low bioavailability (< 4% in rat and monkey). Less than 1% excretion in urine. Activity comparable to ezetimibe (^{14}C-cholesterol excretion and LDL lowering effect). More effective than ezetimibe in preventing atherosclerosis in APOE*3 Leiden mice: significantly reduced inflammation markers (SAA, MCP-1, E-selectin, VCAM-1) in plasma (all p< 0.01); reduced fibrinogen (by 32%) and hepatic cholesterol content (by 69%, p< 0.05). (ezetimibe: No effect on fibrinogen levels and smaller effect on hepatic cholesterol content); and strongly inhibited atherosclerosis development (lesion size, by 93%, and lesion number, by 61% (all p< 0.001). Formulation: one tablet, once a day with dinner (standalone tablet and fixed dose combination with atorvastatin). Most advanced development phase: phase III interim analysis.
Safety/Tolerability	No genotoxicity, reproductive toxicity or safety pharmacology findings. Repeat-dose toxicology up to 6 months in rats and up to 12 months in monkeys; no systemic effects (NOAELs = 2000 mg/kg/day). A 28-day i.v. study in rats: no AEs. 3-Month Combination Toxicity with Atorvastatin: No difference. No effect on gastrointestinal transit. Absence of drug-drug interactions. No “caution” in patients with moderate to severe hepatic impairment. Good safety profile: No/minimal systemic toxicity. Good tolerability expected in combination with statin therapy.
Additional Information	Phase 1 SAD in healthy volunteers (HVs): safe and well tolerated up to 200 mg. Exposure levels < lower limit of quantitation (1.0 ng/ml). Pilot food effect: plasma concentrations < 1.0 ng/ml also in fed conditions and safety/tolerability not impacted by food. BEX in HVs: less than 1% of dose found in urine; 92% of dose excreted unchanged in feces. Little metabolic degradation (two cleavage products). No clinically significant PK interaction w/ oral contraceptives, atorvastatin, simvastatin or rosuvastatin in HVs. Phase 2: LDL reduction -12.2 % after 50 mg QD (AM) and -14.5% after 25 mg QD (PM). Discontinued due to limited efficacy in Phase 3 interim analysis: effect size (QD) lower than 15%.
Suitable for and Exclusions	
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=ave5530
Publications	None