SANOFI	AVE5530/canosimibe
Mechanism of Action	Acyl-coenzyme A: Cholesterol *O*-Acyltransferase inhibitor; cholesterol absorption inhibitor http://www.ncbi.nlm.nih.gov/gene/38
Overview	Pre-systemic inhibition of intestinal cholesterol absorption. Canosimibe is 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 [serum amyloid A (SAA), monocyte chemoattractant protein (MCP-1), endothelial (E) -selectin, vascular cell adhesion molecule (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. 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 3 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 adverse events. Three-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 single ascending dose in healthy volunteers (HV): safe and well tolerated up to 200 mg (single dose). Exposure levels < LLOQ (1.0 ng/ml). Pilot food effect: plasma concentrations < 1.0 ng/ml also in fed conditions and safety/tolerability not impacted by food. Radiolabeled mass balance study (BEX) in HV: 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 with oral contraceptives, atorvastatin, simvastatin or rosuvastatin in HV. Phase 2: LDL reduction -12.2% after 50 mg every day, morning (QD-AM) and -14.5% after 25 mg (QD-PM). Discontinued due to limited efficacy in Phase 3 interim analysis: Effect size after 3 months of daily administration was less than 15%.
Suitable for and Exclusions	All studies conducted in adults. No juvenile toxicity studies conducted.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=ave5530
Additional Characteristics: CNS Penetrance/Pediatric Diseases	Not suitable for CNS. Pediatric studies that will be considered: new indications, in which the benefit to the patient is not driven by magnitude of LDL reduction.
Publications	N/A