Sanofi	AVE8134
Mechanism of Action	Peroxisome proliferator-activated receptor α (PPARα)/nuclear receptor 1C1 (NR1C1) agonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=593&familyId=86 http://www.ncbi.nlm.nih.gov/gene/5465
Overview	AVE8134 is an orally active, novel potent PPARα agonist intended for the treatment of type 2 diabetes/insulin resistance and mixed dyslipidemia. Preclinical results from animal models of T2DM demonstrated reductions of free fatty acids, blood glucose and HbA1c. AVE8134 showed positve effects in different rodent heart failure models at doses below the doses necessary for antidiabetic effects.
Safety/Tolerability	In Phase 1, possibly drug related CK increases were seen at 30 mg. The subjective observations at the 10 mg doses were ambiguous. Therefore, it seems possible to establish a therapeutic margin. In the ACT6355 study it was demonstrated that musculoskeletal safety can be monitored.
Additional Information	The target indication for AVE8134 is type 2 diabetes (T2DM). In healthy volunteers, repeated administration of AVE8134 lowered triglycerides (TGs) at doses of 10 mg/day and higher and at 20 mg/day and higher increased HDL levels. Effects on blood glucose are expected to require higher doses than those required for lipid reductions. AVE8134 was safe and well-tolerated up to doses of 20 mg, although some subjects experienced muscle and back pain at a dose of 10 mg. At 30 mg mild increases of CPK were observed, which were interpreted as possible signals of myotoxicity. A 3 month phase II study (ACT6355) in diabetic patients, including those treated with statins, was performed with 1mg/day. Based on the low dose, no any efficacy endpoint was met with AVE8134. Safety profiles were similar between AVE8134 and placebo. The clinical relevance of PPARα agonists for glycemic control has not been demonstrated for any PPARα agonist so far. The relevance of the target remains to be shown.
Suitable for and Exclusions	The treatment in T2DM is chronic, requiring demonstration of chronic use safety. Carcinogenicity will have to be completed before the start of Phase 3.
Clinical Trials	http://apps.who.int/trialsearch/trial.aspx?trialid=EUCTR2005-005141-19-IT
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AVE8134