SYNOPSIS

Name of company: sanofi-aventis **Name of finished product:** Not available **Name of active substance(s):** AVE8134	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER:** Not applicable **Volume:** Not applicable **Page:** Not applicable	**(For National Authority Use only)**

Title of the study: A 12-week, multicenter, double blind, placebo-controlled, randomized study of the efficacy and safety of 1.0 mg AVE8134 tablets for reducing A1c in the treatment of patients with confirmed type 2 diabetes mellitus who are not on current drug therapy (ACT6355).

Investigator: [redacted]

Study center(s): There were 46 active sites in 10 countries (Chile, Italy, Germany, Korea, Mexico, Poland, Romania, Russia, South Africa, and Spain).

Publications (reference): There has been no publication based on the study to date.

Study period:

Date first patient enrolled: 17 March 2006

Date last patient completed: 15 May 2007

Phase of development: Phase II

Objectives: Primary: determine the effect of AVE8134 on glycemic control measured by the absolute change in glycosylated hemoglobin (HbA1c also known as A1c) from baseline to endpoint. Secondary: investigate the effects of AVE8134 on fasted plasma glucose (FPG), the change of the glucose profile on select days, fasted insulin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), fasted serum triglycerides, total cholesterol (Total C), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein (VLDL), free fatty acids (FFA), high-sensitivity C-reactive protein (hsCRP), adiponectin, apolipoprotein, and body weight and demonstrate the safety of AVE8134 when administered as single daily oral dose over 12 weeks.

Methodology: Multicenter, randomized, double-blind, placebo-controlled, parallel group

Number of patients: Planned: approximately 250 patients in approximately 45 sites globally. Actual: 256 patients in 46 sites.

Randomized: 256

Treated: 256

Evaluated:

Efficacy: 250 (intent-to-treat population)

Safety: 256

Diagnosis and criteria for inclusion:

• Men or women ≥18 years of age who have confirmed type 2 diabetes mellitus as established in the medical history (ie, diagnosed before the screening visit) and have either previously not been treated or are currently not on drug therapy;

• HbA1c ≥7.0 % and ≤10.0 % at screening visit

• FPG between 126 and 250 mg/dL, measured at screening visit.

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Investigational product: AVE8134 Dose: 1 mg tablets Administration: oral, once daily Batch number(s): [redacted]		
Duration of treatment: 12 weeks **Duration of observation:** approximately 13-14 weeks (1 week screening, 12 weeks double-blind treatment, and 3 days follow-up for safety, treatment-emergent adverse events [TEAE])		
Reference therapy: Placebo Administration: oral, once daily Batch number(s): [redacted]		
Criteria for evaluation:		
Efficacy: Primary: change from baseline to week 12/Visit 14 in HbA1c. Secondary: change from baseline to week 12/Visit 14 in: FPG and glucose profiles on select days (see study schedule), fasted insulin, HOMA-IR, fasted serum triglycerides, fasted Total C, HDL-C, LDL-C, VLDL, FFA, hsCRP, adiponectin, apolipoprotein, body weight. Safety: Adverse events (AEs) and other safety information (clinical laboratory evaluations, vital signs, and ECG). Symptoms and signs of hypoglycemia and myopathy (including creatinekinase [CK] elevation) were closely monitored.		

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Statistical methods: Unless otherwise specified, all statistical tests were two-sided, at a nominal 5% significance level. Continuous data were summarized for each treatment group using the number of observations available (N), means, standard deviation (SD), minimums, medians, and maximums. Categorical data were summarized for each treatment group using counts and percentages.

Primary efficacy variable The primary endpoint, change from baseline to Week 12 in HbA1c, was analyzed using ANCOVA with treatment (AVE8134 or placebo), randomization stratum (use/no use of statin at screening visit), and country as fixed effects and using baseline assessment as the covariate. Both means and adjusted means were provided as well as 95% confidence intervals (CI) constructed for adjusted mean differences between AVE8134 and placebo. Primary analysis was performed using the intent-to-treat (ITT) population. The following analyses were also be conducted on HbA1c:

- The main analysis was repeated using the same model on the per protocol (PP) population.
- Categorical analyses were performed on HbA1c level at Week 12 (eg, proportion of patients with HbA1c<7% at Week 12) and on change from baseline in HbA1c at Week 12 (eg, proportion of patients with a decrease ≥ 0.7%). Comparisons between AVE8134 and placebo were done using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum and country. In case of sparse cells, Fisher's exact test was used.

Subgroup analyses were performed on the primary endpoint to assess the homogeneity of treatment difference across subpopulations defined by race, age, gender, BMI, and use/no use of statin at screening.

Secondary efficacy variable Main secondary variables included fasted plasma glucose (FPG), 4-point glucose profiles, fasted plasma insulin, HOMA analysis parameters (insulin resistance, β-cell function), and fasted lipids parameters (TG, Total-C, HDL-C, LDL-C, VLDL). Other secondary variables included fasted FFA, hsCRP, adiponectin, and apolipoprotein. Statistical analysis of all secondary continuous variables was done using the same ANCOVA model as for the primary variable. Categorical secondary efficacy endpoints were analyzed using a CMH test stratified by randomization stratum and country. In case of sparse cells, Fisher's exact test was used. The statistical comparison between AVE8134 and placebo was performed at Week 12 on the ITT population.

Safety variables The safety analysis was based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs, and ECG) and performed on the safety population. The commonly reported AEs were also summarized according to demographic factors (gender, age) and use/no use of statin for each treatment group. Predefined thresholds for Potentially Clinically Significant Abnormalities (PCSAs) in laboratory parameters and vital signs were used. Counts of treatment-emergent adverse events (TEAEs) were provided for each preferred term (PT) within each system organ class (SOC). Common (>1% in any treatment group) and very common (>5% in any treatment group) TEAEs were summarized and described with reference to demographic factors, time to onset, maximal intensity, and relation to treatment. Specific events of interest related to myopathy and/or CK elevations were analyzed and summarized. Deaths, other serious adverse events (SAEs), and AEs leading to treatment discontinuation were summarized and presented as number and percent of patients in each randomized treatment group. Both quantitative and qualitative approaches were used to analyze the laboratory data. The overall incidence of PCSAs during the double-blind treatment period was summarized for each laboratory test, vital sign, and treatment group. As a parameter of special interest, CK elevations were analyzed as a categorical analysis. Descriptive statistics was used to summarize laboratory and vital sign results and their change from baseline values by visit and treatment group. ECG abnormalities were summarized for each treatment group using counts and percentages; statistical analysis was not performed. A summary of safety results was presented for each treatment group.

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Summary:

Efficacy results:
1) AVE8134 1 mg did not reduce HBA1C compared with placebo. Specifically, there was no measured difference in insulin resistance or beta-cell function at 3 months.
2) Similarly, AVE8134 1 mg did not show activity compared to placebo in any of secondary analyses.

Safety results:
There was no adverse event signal in any laboratory parameter or vital signs, eg heart rate, systolic or diastolic blood pressure. There was no adverse effect on body weight during the course of the study. There were no reports of heart failure or cardiac ischemic events. There were no reported deaths during this study.

Conclusions: [redacted]

Date of report: 15-Jan-2008