SYNOPSIS

Name of company: sanofi-aventis **Name of finished product:** AVE0010 **Name of active substance(s):** Not applicable	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER:** **Volume:** **Page:**	**(For National Authority Use only)**

Title of the study: A randomized, double-blind, placebo-controlled, multinational study evaluating the safety and pharmacokinetics of 5 and 10 µg AVE0010 single doses and the efficacy, safety and pharmacokinetics of AVE0010 administered for 5 or 6 weeks, either once or twice daily, following dose escalation from 5 to 30 µg in Japanese and Caucasian type 2 diabetic patients not adequately controlled with sulfonylurea or sulfonylurea and metformin (PDY6797)

Investigator(s): [redacted]

Study center(s): The study was conducted in 30 centers in 5 countries

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 03/Nov/2006

Date last patient completed: 16/Sep/2007

Phase of development: Phase II

Objectives: The primary objective of the study was to assess the effects of individually stepwise increasing once daily (QD) and twice daily (BID) doses of AVE0010 on the increase in plasma glucose concentration induced by a standardized breakfast test meal at the highest tolerated dose of AVE0010 in type 2 diabetic patients.

The main secondary objectives of the study were to assess the treatment by ethnicity interaction of individually increasing QD and BID doses of AVE0010 on the increase in plasma glucose concentration induced by a standardized breakfast test meal between Japanese and Caucasian type 2 diabetic patients at the highest tolerated doses of AVE0010, and to assess the safety, tolerability and pharmacokinetics of 5 and 10 µg single doses of AVE0010.

The other secondary objectives of the study were to assess the effects of individually stepwise increasing QD and BID doses of AVE0010 in Japanese and Caucasian patients on pharmacodynamic, safety, tolerability and pharmacokinetics parameters of AVE0010.

Methodology: A randomized, double blind, placebo-controlled, combined single-dose and repeated-dose escalation, parallel-group design study conducted both in Japanese and Caucasian patients.

Number of patients: Planned: 120 (60 Japanese and 60 Caucasian)

Randomized: 120 (63 Japanese and 57 Caucasian)

Treated: 120

Evaluated:

Efficacy: 110 (Per-protocol population); 119 (Modified intent-to-treat [mITT] population)

Safety: 120

Pharmacokinetics: 120 (including placebo)

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Diagnosis and criteria for inclusion:

Japanese or Caucasian males or females patients aged 20 to 75 years at the time of screening. Female patients must be post-menopausal with at least 12 months amenorrhea or surgically sterile for at least 3 months prior to the time of screening. Japanese patients living outside Japan were defined as: 1) having Japanese nationality; 2) parents both Japanese; 3) living outside Japan for no longer than 5 years. Caucasian patients were defined as white patients having both parents as white of caucasian origin.

Type 2 diabetes mellitus diagnosed for at least one year prior to the time of screening as established in the medical history and defined by American Diabetes Association criteria.

Stable type 2 diabetes mellitus treated either with sulfonylurea alone or sulfonylurea and metformin at a stable dose for at least 3 months prior to the time of screening and no other antidiabetic medications for at least 3 months prior to the screening.

Body mass index (BMI) ≤ 35 kg/m² at the time of screening.

Glycosylated hemoglobin (HbA1c) ≥7.0% and ≤10.0% at the time of screening.

Fasting plasma glucose at screening between 108-250 mg/dL (6.0-13.9 mmol/L).

Investigational product: AVE0010

Dose: Single dose period; 5 µg or 10 µg.

Repeated dose-escalation period; starting dose 5 µg QD or BID increased every week in 5 µg increments up to a total of 30 µg daily in the QD group and 60 µg daily in the BID group,

or starting dose 10 µg QD or BID increased every week in 5 µg increments up to a total of 30 µg daily in the QD group and 60 µg daily in the BID group.

Patients in the QD group received AVE0010 in the morning and placebo in the evening and patients in the BID group received AVE0010 in the morning and evening.

Administration: Subcutaneous (SC) injections, 30 minutes before morning and evening meals

Batch number(s): [redacted]

Duration of treatment: 1 day during the single dose period. During repeated dose-escalation period; 6 weeks ± 2 days (1st cohort: 5 µg/injection starting dose level) and 5 weeks ± 2 days (2nd cohort: 10 µg/injection starting dose level)

Duration of observation: Total duration per patient: 61 ± 5 days (2nd cohort) or 68 ± 5 days (1st cohort)

Reference therapy: Placebo

Dose: Volume matching verum

Administration: Subcutaneous (SC) injections, 30 minutes before morning and/or evening meals

Batch number(s): [redacted]

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Criteria for evaluation:

Efficacy: The primary efficacy variable was the change from baseline in the $AUC_{[0:29h-4:30h]}$ (h*mg/dL) of the postprandial plasma glucose after a standardized breakfast meal test on the last day at the highest well tolerated dose.

Secondary efficacy variables were:

The change from baseline in the $AUC_{[0:29h\ 4:30h]}$ (h*mg/dL) of the postprandial plasma glucose, insulin and glucagon after a standardized breakfast meal test on the last day of the respective actual doses of 10, 20, and 30 µg;

The change from baseline in two-hour postprandial plasma glucose (mg/dL) after a standardized breakfast meal test and after dinner, respectively, on the last day of the respective actual doses of 10, 20, and 30 µg or on the last day at the highest well tolerated dose;

The change from baseline in fasting plasma glucose (mg/dL), fasting insulin (µU/mL), fasting glucagon (pg/mL), fructosamine (µmol/L), HbA1c (%), and weight (kg) on the last day at the highest well tolerated dose.

Safety: Adverse events (AEs) including injection site reactions, vital signs (blood pressure and heart rate), 12-lead ECG, laboratory tests (hematology and serum chemistry), hypoglycemia, and concentration of anti-AVE0010 antibodies in the plasma.

Pharmacokinetics:

Single dose phase

Concentration of AVE0010 in plasma up to 24h post-injection.

Repeated-dose phase

Concentration of AVE0010 in plasma up to 10 hours post-morning injection and 2.5 hours post-evening injection on the last day of 10, 20, and 30 µg/injection (or at the highest well tolerated dose) levels, respective doses summarized non-compartmentally by the following parameters (*in case of BID dosing: for the morning dose only with τ=10 h)*:

$AUC_{(\tau),ss}$, $C_{max(\tau),ss}$, $t_{max(\tau),ss}$, $t_{1/2(\tau),ss}$

Urine concentration of AVE0010.

Pharmacokinetic sampling times and bioanalytical methods:

Pharmacokinetic samples in plasma were collected as follows:

Single-dose phase: at 0.0 (pre-injection), 0.5, 1.0, 1.5, 2.0, 2.5, 3.5, 4.5, 6.5, 10, 12.5, and 24 h post-injection.

Repeated-dose phase: at 0.0 (pre morning-injection), 0.5, 1.0, 1.5, 2.0, 2.5, 3.5, 4.5, 6.5, and 10.0 h post-morning injection and 2.5 h post-evening injection.

The concentration of AVE0010 in plasma was analyzed using a validated sandwich immunoassay method. The lower limit of quantification for AVE0010 was 12 pg/mL.
In the morning of each profile day a blood sample was collected to determine anti-AVE0010 antibodies.

Urine samples were collected in the 10-hour dosing interval between morning and evening dose, at Baseline (D-1), and on each profile day (ie, last day of 10, 20, and 30 µg dosing). The concentration of AVE0010 in urine was analyzed using the same validated immunoassay method as used for plasma analysis. The lower limit of quantification for AVE0010 was 240 pg/mL due to the fact that urine samples were diluted 1:20 in human EDTA plasma prior to analysis. Due to dilution with human EDTA plasma the sample matrix was adjusted to the matrix of the calibrators and the assay can be regarded as validated.

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Statistical methods:

All pharmacokinetic parameters of AVE0010 in plasma were summarized separately by ethnicity, dose, and antibody status.

The primary efficacy analysis was performed for the primary efficacy variable by using the ANCOVA model with treatment, cohort, ethnicity and interaction of treatment by ethnicity as fixed factors and using baseline value as a covariate based on Per-protocol population.

The adjusted means, the 95% confidence intervals for adjusted means and p-values for the comparisons of AVE0010 QD versus placebo and AVE0010 BID versus placebo, respectively, were obtained by ethnicity and overall.

Potential treatment-by-ethnicity interaction was tested using the above ANCOVA model.

The other secondary efficacy variables were analyzed using the same model as described above for the primary efficacy variable.

In addition, pharmacodynamic variables were summarized using the following descriptive statistics applied on the absolute values and the change from baseline: number of subjects (N), mean, standard deviation, median, minimum and maximum.

The blood glucose AUC/the relevant dosage at the end of each dose level were summarized for each ethnicity to assess dose-response relationship.

Treatment effect similarity between the two ethnicities was based on efficacy, safety, and PK/PD analyses.

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Summary:

Efficacy results:

For the per protocol population, pairwise adjusted mean differences vs. placebo for the primary efficacy variable, the change from baseline in $AUC_{[0:29h-4:30h]}$ of postprandial plasma glucose, were -333.4 and -288.8 h*mg/dL in the AVE0010 QD and BID groups, respectively. This was highly significant for the QD and BID group in comparison with placebo.

For Japanese patients, pairwise adjusted mean differences vs. placebo for the primary efficacy variable was -406.7 and -346.3 h*mg/dL and for Caucasian patients -260.1 and -231.3 h*mg/dL in the AVE0010 QD and BID groups, respectively. These differences in comparison with placebo in both, the AVE0010 QD and BID groups for each ethnicity, were highly significant.

For the primary efficacy variable $AUC_{[0:29h-4:30h]}$ of postprandial plasma glucose, the treatment by ethnicity interaction test was statistically significant (p=0.0074) . This interaction was quantitative, that is, the treatment effects of AVE0010 were observed for each ethnicity, however, the magnitude of AVE0010 effect was greater in Japanese than in Caucasian.

Safety results:

No deaths occurred during the study and no severe hypoglycemia events were reported. Two (2) serious adverse events (SAEs) occurred in the Caucasian ethnicity (1 in the placebo and 1 in the AVE0010 BID group) after the first dosing (1 atrioventricular block second degree and 1 coronary artery disease). Both SAEs led to permanent discontinuation of the treatment. The causal relationship to study drug assessed by the investigator for both SAEs was not reasonable, and the causal relationship assessed by the company for both SAEs was excluded. In addition, 1 patient in the Japanese ethnicity BID group had 1 treatment emergent adverse event (TEAE) leading to permanent treatment discontinuation (viral gastroenteritis occurring during repeated dose period).

The numbers and percentages of patients with TEAEs were similar in Japanese and Caucasian AVE0010 QD and BID groups. Gastrointestinal disorders with nausea, vomiting and diarrhea were the most frequent TEAEs reported. Overall, for safety no relevant difference between both ethnicities was detected.

As expected for this substance, patients developed antibodies against AVE0010. Between both ethnicities there was no relevant difference observed: 11 (26.2%) Japanese and 11(28.9%) Caucasian patients were anti-AVE0010 antibody positive at the end of treatment.

Pharmacokinetic results:

In antibody negative patients not requiring a dose reduction, the mean $AUC_{(\tau),ss}$ for 10/20/30 µg in the QD regimen was 367/869/1100 pg*h/ml and 325/941/574 pg*h/ml, for Japanese and Caucasian patients respectively; the respective mean C_{max} values were 80.4/172/194 pg/ml respectively 61.6/133/95.8 pg/ml. The exposure for the BID regimen (morning dose) is similar. Both for single-dose and repeated-dose phase, drug exposure increased with dose in Japanese and Caucasian ethnicity, except for the QD regimen in AVE0010 antibody-negative Caucasian patients.

In both ethnicities, the variability of PK parameters was relatively high, and the exposure was similar and highly overlapping. The difference observed for the exposure was probably based on the difference in body weight between the two populations (mean at baseline for Japanese 66 kg vs. Caucasian 86 kg).

In the presence of anti-AVE0010 antibody, C_{max} and AUC increased compared to antibody-negative situation and varied widely for both ethnicities.

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Conclusions: [redacted]		
Date of report: 12-Mar-2009		