SYNOPSIS

Name of company: sanofi-aventis

Name of finished product: Not applicable

Name of active substance(s): AVE0010

Title of the study: A 13-week Multinational, Randomized, Double-Blind, Placebo-Controlled, Dose-Response Trial Assessing the Safety, Tolerability and Efficacy of AVE0010 in Metformin-Treated Subjects with Type 2 Diabetes Mellitus

Investigator(s): [redacted]

Study center(s): 133 centers in 7 countries

Publications (reference): None

Study period:

Date first subject enrolled: 29 March 2006

Date last subject completed: 01 August 2007

Phase of development: Phase II

Objectives:

Primary: To evaluate the dose-response relationship of AVE0010 administered once daily and twice daily with chronic dosing in metformin-treated subjects with type 2 diabetes

Secondary: To evaluate the efficacy of AVE0010 administered once daily and twice daily with chronic dosing, based on glycemic parameters

To evaluate the safety and tolerability of AVE0010 with chronic dosing

To evaluate the pharmacokinetic profile of AVE0010 with chronic dosing

Methodology: multicenter, placebo-controlled, randomized, parallel-group

Number of subjects: Planned: 500

Randomized: 542

Treated: 542

Evaluated:

Efficacy: 529

Safety: 542

Pharmacokinetics: 311 (128 subjects with standard meal challenge test, 183 without standard meal challenge test)

Pharmacodynamics: 201 subjects with standard meal challenge test

Diagnosis and criteria for inclusion: Males or females aged 30 – 75 years with type 2 diabetes mellitus, pre-treated with metformin at a stable dose of ≥1.0 g/day for at least 3 months prior to screening, with a body mass index of 25 - 40 kg/m^2 and an HbA_{1c} of ≥7.0% and <9.0% at screening

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Investigational product: AVE0010, subcutaneous (s.c.) injection

Dose: 5 µg, 10 µg, 20 µg, or 30 µg, either twice daily (BID) (before breakfast and before dinner), which corresponds to total daily doses of 10 µg, 20 µg, 40 µg, or 60 µg, or once daily (QD) (before breakfast and volume-matched placebo before dinner); subjects randomized to doses of 20 µg or 30 µg were to start with a dose of 10 µg and escalate the dose in weekly 5 µg steps to the assigned dose

Administration: s.c. 0 – 60 minutes prior to breakfast (BID and QD) and dinner (BID only)

Batch number(s): [redacted]

Duration of treatment: including a 2-week run-in period and a 13-week active treatment period

Duration of observation: 15 – 17 weeks (including screening and run-in period)

Reference therapy: Placebo

Dose: Volume-matching AVE0010

Administration: s.c. 0 – 60 minutes prior to breakfast and dinner (placebo groups); s.c. 0 – 60 minutes prior to dinner (AVE0010 QD groups)

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy: HbA_{1c}, plasma fructosamine, fasting plasma glucose (FPG), averaged self-monitored 7-point blood glucose, body weight and waist measurement, lipids

Pharmacodynamics: Standardized meal challenge variables (postprandial plasma glucose and serum insulin, proinsulin, C-peptide and glucagon following a standardized meal challenge test in all subjects in selected sites)

Safety: Adverse events (AEs), serious adverse events (SAEs), hematology, clinical chemistry, AVE0010 antibodies, vital signs, electrocardiogram (ECG)

Pharmacokinetics: Area under curve (AUC) (0-4.5h), C_{max}, t_{max}, C_{trough}

Pharmacokinetic sampling times and bioanalytical methods: prior to the meal test (0 minutes), and at 30, 60, 120, 180, and 240 minutes after the start of the meal test in a subset of about 50% of all subjects at Visit 11 (Week 13). Related to the actual dose this corresponds to predose and 0.5, 1, 1.5, 2.5, 3.5, and 4.5 hours after dosing.
The concentration of AVE0010 in plasma was analyzed using a validated sandwich immunoassay method. The lower limit of quantification (LLOQ) for AVE0010 was 12 pg/mL.
In the morning of Visits 4 (baseline), 8 (week 4), and 11 (week 13), before dosing, a blood sample was collected to determine human anti-AVE0010 antibodies.

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Statistical methods:

Efficacy: The primary efficacy analysis was the analysis of the change in HbA_{1c} from baseline to endpoint. The primary statistical model for the change in HbA_{1c} from baseline to endpoint was an ANCOVA model with treatment and country as fixed factors and baseline HbA_{1c} as a covariate. Summary statistics were provided including 95% confidence intervals (CIs) for adjusted mean differences between active treatments and placebo. A step-down trend test procedure was applied to account for multiple testing. Continuous secondary efficacy variables were analyzed using the same methods as for the primary efficacy variable. Frequency distributions were presented for categorical efficacy variables, which were tested using a Cochran-Mantel-Haenszel (CMH) test stratified by country. Appropriate graphical presentations were generated. HbA_{1c} changes from baseline were also analyzed by anti-AVE0010 antibody status (positive, negative).

Safety: All safety presentations were generated using standard tables as applicable and were based on the safety population. With regard to AEs, the focus was on treatment-emergent adverse events (TEAEs). No statistical tests were performed for the analysis of AEs. Descriptive statistics were presented for laboratory variables, including frequency distributions and shift tables for potentially clinically significant abnormalities (PCSAs). Vital signs and findings from the physical examination and ECG assessment were descriptively summarized.

Pharmacokinetics: Plasma concentrations were summarized by mean, SD, coefficient of variation, minimum and maximum, and geometric mean for each time point by treatment group and by antibody status. Individual AVE0010 concentrations as well as mean values per treatment group were plotted against time for the AVE0010 treatment group (using the per protocol [PP] sampling times). Log-transformed AUC(0-4.5h) and C_{max} were analyzed by an ANOVA model with treatment as a factor. Geometric mean and associated 95% CI for AUC(0-4.5h) and C_{max} were provided for each treatment group based on the ANOVA model.

The t_{max} was subjected to a non-parametric analysis. Non-parametric 95% CIs for the median were calculated by treatment group. The PK parameters were also summarized by antibody status (negative, positive, positive with high PK, positive with normal PK).

Pharmacodynamics: The change in pharmacodynamic (PD) parameters from baseline to Week 13 was analyzed and treatment comparisons assessed using an ANCOVA model with treatment and country as fixed factors and the baseline PD value as a covariate, in a substudy for subjects undergoing a meal test (all subjects in selected sites). The estimates and the corresponding 95% CIs for the comparisons of each AVE0010 arm versus placebo were provided along with adjusted means and standard errors for each treatment group.

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Summary:

Efficacy/pharmacodynamic results:

For the primary variable HbA_{1c}, a dose-response relationship was seen within each regimen (QD and BID). The step down linear trend tests for all treatment groups versus placebo were highly significant. Corresponding pair-wise adjusted mean differences versus placebo (95% CIs) ranged from -0.28% (-0.47%, -0.09%) in the 5 µg QD group to -0.69% (-0.88%, -0.49%) in the 30 µg BID group. The reduction of HbA_{1c} from baseline to endpoint reached a maximum at the 30 µg dose level (BID or QD), but compared to the 20 µg dose levels the added benefit of the highest dose was not clinically relevant (-0.50 and -0.57% with 20 µg and 30 µg AVE0010 QD, respectively, and -0.57 and -0.69% with 20 µg and 30 µg AVE0010 BID, respectively). Moreover, the 10 µg BID and 20 µg QD (similar daily doses) did not show clinically relevant differences in terms of HbA_{1c} reductions (-0.59 and -0.50% placebo-subtracted decreases from baseline, respectively).

Results from a categorical analysis of HbA_{1c} were consistent with those from the primary analysis. Pair-wise comparisons versus placebo for the percentages of subjects with HbA_{1c} <7.0% at endpoint (ie, number of responders) were all statistically significant (ranging from 47 to 69% with QD dosing and from 51 to 77% with BID dosing). Only a small further increase in the 30 µg dose level compared to the 20 µg dose was observed in the QD regimen (68.6 and 67.9%, respectively), whereas slightly less subjects were responders (64.8%) in the 10 µg BID group. The highest number of responder subjects was in the 30 µg BID group (77.4%).

Further improvement in glycemic control to HbA_{1c} <6.5% at study end was observed in significantly more patients in the AVE0010 groups than in the placebo group (7.5%), with one-third of patients receiving 20 or 30 µg QD, 5, 10, and 20 µg BID, and 43.4% of the patients receiving 30 µg BID achieving this target.

As expected for a peptide, subjects developed antibodies against AVE0010, between n=22 (43.1%) in the AVE0010 10 µg QD group and n=37 (71.2%) in the 20 µg BID group. Nevertheless, no apparent relationship was observed between the anti-AVE0010 antibody status (ie, antibody positive or negative) and HbA_{1c} changes from baseline at study end.

Fasting plasma glucose (FPG) decreases were dose-dependent, reaching the maximum effect at the 30 µg dose level (either BID or QD). In the AVE0010 groups, LS mean changes from baseline to endpoint in FPG ranged from 0.19 mmol/L (5 µg BID group) to 1.42 mmol/L (30 µg BID group), compared to -0.21 mmol/L in the placebo group. The step down linear trend tests versus placebo were statistically significant for the 30 µg QD, 10 µg BID, 20 µg BID and 30 µg BID groups. The 20 µg QD was close but did not reach the statistical significance at study end (the placebo-subtracted FPG decrease was -0.59 mmol/L, p=0.0533).

A dose-response relationship with both regimens and with all doses was seen for the 2-hour post-prandial (after breakfast) and AUC(0-4h) plasma glucose. A statistically significant dose-response relationship was observed for post-prandial serum insulin AUC(0-4h), as well as for 2-hour post-prandial serum insulin in the 20 and 30 µg QD and 30 µg BID groups, and for C-peptide in the highest QD dose groups (20 and 30µg). Two-hour post-prandial glucagon decreased significantly in all AVE0010 groups except in the 5 µg QD group.

A dose-response relationship with both regimens was seen in the averaged 7-point self-monitored blood glucose profiles, however, the placebo-subtracted decreases from baseline were similar in the 20 and 30µg QD groups (–1.21 and -1.34 mmol/L, respectively) and did not seem better in the 10 µg BID group (-1.07 mmol/L). The 20 and 30 µg BID groups showed slightly higher decreases from baseline (-1.30 and -1.55 mmol/L, respectively).

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Placebo-subtracted weight decreases from baseline were higher in the QD groups than in the corresponding BID groups (except for the 30µg BID group), and in particular with the 20 µg QD as compared with 10µg BID group. The doses of the 20 µg QD, 30 µg QD, and 30 µg BID showed significant differences compared to placebo (corresponding adjusted mean differences versus placebo and 95% CIs ranged from -1.07 kg [-1.92 kg, -0.22 kg] in the 20 µg QD group to -1.95 kg [-2.79 kg, -1.10 kg] in the 30 µg BID group). A clear dose-response relationship was observed for each regimen, ie, the higher the AVE0010 dose within a regimen (QD or BID) the larger was the mean decrease in body weight.

For waist circumference, doses of 10 µg and 30 µg BID showed significant decreases at study end.

Safety results:

There was no relevant difference between regimens (QD or BID) in the reporting of TEAEs, however, the percentage of subjects with TEAEs was dose-dependent within each regimen. Most reports were from the system organ class of Gastrointestinal disorders, with the most frequently reported TEAE being nausea. A clear dose-response relationship within both regimens was seen in the number of subjects with nausea: frequencies ranged from 7.3% (5 µg) to 35.2% (30 µg) in AVE0010 QD groups (25.5% with 20 µg QD) and from 7.5% (5 µg) to 33.3% (30 µg) in AVE0010 BID groups (14.3% with 10 µg BID). Other frequently reported TEAEs included diarrhea, vomiting, headache, and dizziness. For diarrhea, a significant increase of incidence was observed with 30 µg BID (25.9% of the subjects), whereas the incidence was much lower with both 20 µg QD and 10 µg BID (9.1% and 7.1%, respectively). For vomiting, a significant increase of the incidence was reported with 30 µg QD (18.5%), whereas it was 5.5% and 7.1% with 20 µg QD and 10 µg BID, respectively. The onset of the gastrointestinal TEAE episodes (nausea, vomiting, diarrhea) decreased with time (appeared mostly during the first 3 to 6 weeks of the treatment), and were usually mild to moderate in intensity.

A total of 11 subjects (8 in the AVE0010 groups and 3 in the placebo group) and no more than 3 subjects in any treatment group reported at least 1 SAE during the on-treatment period of the study.

The number of subjects with permanent treatment discontinuations for TEAEs was low in the 5, 10 and 20 µg QD and 5 and 10 µg BID groups (0 to 2 subjects in each group), and 2 subjects in the placebo group, but it increased in the 30 µg QD and BID groups (6 and 4 subjects, respectively) and in the 20 µg BID group (8 subjects), mainly due to gastrointestinal adverse events.

In the AVE0010 groups, 1 to 2 subjects in the AVE0010 QD groups and 1 to 3 subjects in the AVE0010 BID groups reported at least 1 symptomatic hypoglycemia, compared to 1 subject (0.9%) in the placebo group. No severe hypoglycemia events were reported during the study.

No relevant differences between treatment groups or findings of concern were observed in the analyses of laboratory values, vital signs, ECG assessments, or physical examination.

For 520 subjects in the safety population, an anti-AVE0010 antibody status was available; among these, 250 subjects (48.1%) were antibody-positive and 270 (51.9%) were antibody-negative at study end with no dose relationship. No apparent relationship was observed between the antibody status and safety and tolerability.

Pharmacokinetic results:

The drug exposure increased with dose for the QD and BID regimens. Dose proportionality was statistically explored for each regimen (ie, QD and BID) using pair-wise dose-adjusted AUC(0-4.5h) and C_{max} ratios in an ANOVA model with treatment included as a fixed effect for antibody negative and antibody positive subjects. Except when comparing C_{max} over the complete dose range (30 µg versus 5 µg) in anti-AVE0010 antibody-negative subjects of the QD groups, for all other treatment groups the respective dose adjusted C_{max} and AUC(0-4.5h) ratios suggested proportionality between PK and dose, bearing the limitation of small sample size in some of the groups.

The variability of the exposure after chronic dosing was low to moderate for antibody negative subjects, but it strongly increased for antibody positive subjects.

In the subpopulation with extensive PK assessment (ie, in subjects with standard meal challenge test) antibodies were present in 42% of the subjects in the QD regimen, and 73% of the subjects in the BID regimen.

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Conclusions: [redacted]

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