SYNOPSIS

Title of the study: A randomized, double-blind, parallel-group, placebo-controlled, dose-response, multicentre, multinational study evaluating the efficacy and safety of AVE2268 administered either twice daily (breakfast and lunch) at a dose of 300, 600 and 1200 mg or once daily (breakfast) at a dose of 1200 mg, in patients with type 2 diabetes treated with metformin and not adequately controlled. (DRI6738)

Coordinating Investigator(s): Not applicable

Study center(s): 38 centers with at least 1 patient randomized, in 11 countries (Argentina, Australia, Belgium, Chile, Denmark, France, Germany, Italy, Poland, South Africa, The Netherlands)

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 10 July 2006

Date last patient completed: 24 January 2008

Phase of development: Dose-ranging

Objectives: The primary objective of this study was to demonstrate the efficacy of AVE2268 in reducing mean plasma glucose calculated from 10-point plasma glucose profiles after a 4-week treatment period.
The secondary objectives of this study were to assess the effects of AVE2268 on fasting plasma glucose, 2-hour postprandial plasma glucose (after standardized test breakfast, lunch, and dinner test meals), HbA1c, and fructosamine, and to assess the safety and tolerability of AVE2268 over a period of 4 weeks.

Methodology: multicenter, multinational, 4-week, fixed dose (300, 600, or 1200 mg twice daily or 1200 mg once daily), placebo-controlled, randomized, double-blind, parallel-group, in patients with type 2 diabetes treated with metformin and not adequately controlled

Number of patients: Planned: 300

Randomized: 317

Treated: 316

Evaluated:

Efficacy: 278

Safety: 316

Pharmacokinetics: 158

Diagnosis and criteria for inclusion: Age ≥18 and <75 years; type 2 diabetes mellitus (T2DM) patient for at least 1 year; HbA1c in the range of ≥7.0% and ≤9.0% (per Protocol Amendment No. 5: ≥6.8% and ≤9.2%); for at least 3 months prior to enrollment, stable metformin treatment (dose ≥1.5 g/day) and no other antidiabetic medication; no history or presence of relevant renal or urinary disease.

Investigational product: AVE2268, film-coated tablets of 300 and 600 mg

Dose: 300, 600, or 1200 mg twice daily (BID) or 1200 mg once daily (QD)

Administration: orally with approximately 150 mL of water, 30 min before breakfast and lunch

Batch number(s): [redacted]

Duration of treatment: 4 weeks

Duration of observation: 6 weeks ±8 days (including 1-week screening, 4-week treatment, and 1-week follow-up)

Reference therapy: Placebo, film-coated tablets matching active treatment

Dose: 0 mg

Administration: orally with approximately 150 mL of water, 30 min before breakfast and lunch

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy and pharmacodynamics:

Primary efficacy: change in mean plasma glucose (MPG) from baseline to Week 4/End of treatment; MPG calculated from 10-point plasma glucose profiles (before and 90 and 120 min after standardized test breakfast, lunch, and dinner, and at bedtime).

Secondary efficacy: change in fasting plasma glucose from baseline to Week 4/End of treatment; 2-hour postprandial plasma glucose after standardized breakfast, lunch, and dinner at Week 4/End of treatment; change in HbA1c from screening to Week 4/End of treatment; change in fructosamine from baseline to Week 4/End of treatment.

Pharmacodynamics: baseline-subtracted area under the blood glucose concentration time profile (GLU-AUC0-5h; Day 1 breakfast, Day 28 breakfast, and Day 28 lunch); 24-hour glucose clearance (GLU-CL; Days 1 and 28), amount of glucose in urine (GLU-Ae; Day 28).

Safety: Adverse events (AEs; including hypoglycemia) spontaneously reported by the patient or observed by the Investigator, standard hematology and serum chemistry, renal safety parameters, self-monitored 7-point blood glucose profiles, vital signs, weight, physical examination, number of daily mictions and nocturia, standard 12-lead electrocardiograms.

Pharmacokinetics: AVE2268 plasma concentration data were determined on Day 1, Day 14, and Day 28. The pharmacokinetic variables were calculated using standard noncompartmental techniques.

Pharmacokinetic sampling times and bioanalytical methods:

AVE2268 blood samples were collected
- on Day 1 before breakfast treatment dose, just before breakfast, 1.5 and 2 h after breakfast, and before lunch treatment dose;
- on Day 14 before lunch treatment dose (Ctrough);
- on Day 28 before breakfast treatment dose, just before breakfast, 1.5 and 2 h after breakfast; before lunch treatment dose, just before lunch, 1.5 and 2 h after lunch; 5 h after the lunch treatment dose; just before dinner, 1.5 and 2 h after dinner; and at bedtime.

In total 5 AVE2268 blood samples on Day 1, 1 sample on Day 14, and 13 samples on Day 28.

AVE2268 in plasma: a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method was used; samples were measured at the Department of Metabolism & Pharmacokinetics, Sanofi Aventis, Frankfurt, Germany. The lower limit of quantification (LLOQ) was 1 ng/mL.

Statistical methods: The primary analysis was performed on a per-protocol (PP) population. PP population included all randomized and treated patients without any major protocol violation, as defined in the Statistical Analysis Plan.
Analyses of demographics and baseline characteristics, as well as safety analyses, were conducted on the safety population (randomized and treated patients).
All analyses are performed as treated.

Analysis of the primary endpoint (change in MPG from baseline to Week4/End of treatment) was done in the framework of analysis od covariance (ANCOVA) model. The ANCOVA model included change from baseline in MPG as response, treatment as fixed effect (5 levels: 3 BID doses and 1 QD dose of AVE2268, and placebo) and baseline MPG as covariate.

The primary analysis (change in MPG from baseline to Week4/End of treatment) was performed according to the following hierarchical procedure, in order to maintain an overall type I error rate of 5%:

The primary test was a trend test with ordinal contrast [-3, -1, 1, 3]. Monotone dose response among BID doses (trend) hypothesis was as follows:

$H_0 : \mu_0 = \mu_1 = \mu_2 = \mu_3$ versus $H_a : \mu_0 \leq \mu_1 \leq \mu_2 \leq \mu_3$ *with at least 1 strict inequality.*

If this test was significant, H_0 was rejected and H_a was accepted at significance level 5%, and so, $\mu_0 < \mu_3$ (superiority of 1200 mg BID over placebo) could be claimed at significance level 5%. Then, the mid and the low doses were tested versus placebo according to a step-down procedure as follows: the mid dose 600 mg BID was to be compared to placebo at the 5% level. If significance was reached for the 600 mg BID dose, the lowest dose 300 mg BID was to be compared to placebo again at the 5% significance level.

According to the hierarchical procedure, in case of a significant trend test, the 1200 mg BID dose was not formally tested versus placebo; however the corresponding p-value was to be presented for information.

The 1200 mg QD dose was tested separately versus placebo and could be claimed only if the general trend test was significant.

Continuous secondary efficacy parameters were to be analyzed using the same ANCOVA method as the one described for primary efficacy analysis. However, for HbA1c, no trend test was to be performed.

All statistical tests were 2-sided tests at a nominal 5% significance level.

Pharmacodynamics: The individual pharmacodynamic variables were presented in figures and listed together with descriptive statistics by treatment, study day, and dose of day.

Safety: Safety and tolerability data were summarized by treatment group using descriptive statistics. No statistical tests were planned.

Pharmacokinetics: Descriptive statistics of AVE2268 plasma concentration data and AVE2268 pharmacokinetic variables by treatment group and by treatment day were provided.

Summary:

Efficacy and pharmacodynamics results: All AVE2268 regimens significantly decreased MPG relative to placebo; the effect was dose-dependent in the AVE2268 BID groups (trend test p-value = 0.0024). In the BID dose groups, the highest adjusted mean difference relative to placebo was -0.93 mmol/L for the AVE2268 600 mg dose, with the dose response plateauing from 600 to 1200 mg. The highest decrease from baseline was seen in the 1200 mg QD group, with an adjusted mean difference relative to placebo of -1.10 mmol/L (p = 0.0003).

For fasting plasma glucose, the adjusted mean change from baseline was -0.23 mmol/L in the placebo group and ranged from -0.4 to -0.8 mmol/L in the AVE2268 treatment groups.
A significant decrease relative to placebo was observed for 2-hour post-breakfast and 2-hour post-lunch plasma glucose for all AVE2268 doses, with a significant trend test for the BID dose groups (p <0.0001 and p = 0.0052, respectively). The highest decrease was observed for the AVE2268 1200 mg BID and 1200 mg QD dose groups.
Mean baseline HbA1c was 7.71% (standard deviation [SD]: 0.59) with similar values in the 5 treatment groups. The adjusted mean change from baseline was -0.08% for the placebo group and ranged from -0.19 to -0.32% for the AVE2268 groups. The highest difference versus placebo of -0.25% was observed in the AVE2268 1200mg BID group (p = 0.0091).

Mean urinary glucose excretion (UGE) was dose-dependently increased from baseline in the AVE2268 BID groups, ranging from +78.62 to +154.43 mmol/24 h. The maximal UGE at end of treatment was obtained in the 1200 mg BID group (172.06 mmol/24 h corresponding to 31 g/day). This increase in UGE was not associated with an increase in urinary volume.

Safety results: Overall, the number (%) of patients experiencing a treatment emergent adverse event (TEAE) was similar in the active treatment groups and in the placebo group, with a slightly lower number in the 1200 mg BID group.
Three (3) serious TEAEs (treatment emergent SAEs) were reported: 2 in the 300 mg BID group (accidental overdose; heart rate irregular) and 1 in the 1200 mg BID group (renal impairment), with no dose-related trend.
Three (3) patients in the AVE2268 1200 mg BID group discontinued treatment due to an AE: 2 for a TEAE (blood creatinine increased; renal impairment [suspected unexpected serious adverse reaction, SUSAR]), and 1 for renal impairment with an onset before the start of treatment.
No death was reported.
Overall, there was no noteworthy difference in the frequency and type of TEAEs between the active treatment groups and the placebo group. Most TEAEs were within the system organ classes “Gastrointestinal disorders”(most frequent preferred term was “diarrhea”, with a similar incidence in the placebo group and in the active treatment groups) and “Infections and infestations” (most frequent preferred term was “nasopharyngitis”, with a similar distribution across the different treatment groups). Eight (8) patients, all in the active treatment groups, presented with a urinary tract infection (UTI). There was no trend of increasing frequency of UTI with dose of AVE2268. All cases occurred in women, and the frequency observed was consistent with the UTI frequency described for the general female population.

Analysis of renal function markers (serum creatinine, creatinine clearance, proteinuria, albuminuria, β2-microglobulin, N-acetyl-β-glucosaminidase) did not show any particular signal. In this study, after 4 weeks of treatment, there was no evidence suggesting a tubular toxicity.
In the AVE2268 BID treatment groups, there was a dose-dependent decrease in serum uric acid.
A decrease in systolic and diastolic blood pressure was observed in all AVE2268 groups.

Pharmacokinetic results: The mean AVE2268 plasma exposure in T2DM patients after multiple oral doses of AVE2268 (300, 600, or 1200 mg BID or 1200 mg QD) for 4 weeks was in line with a proportionality shape. The median time to maximum AVE2268 plasma concentration was between 0.55 and 0.67 h. There was no indication of AVE2268 accumulation.

Conclusions: [redacted]

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