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Sponsor: Sanofi **Drug substance(s):** AVE0010	**Study Identifiers:** N/A **Study code:** ACT6011
Title of the study: Pharmacodynamics, safety, tolerability and pharmacokinetics following dose titration of subcutaneously administered AVE0010 in patients with type 2 diabetes mellitus in a double-blind, randomized, placebo-controlled Phase IIa study	
Study center(s): Bloemfontein, Cape Town, and Johannesburg, South Africa	
Study period: Date first subject enrolled: 03/May/2004 Date last subject completed: 11/Oct/2004	
Phase of development: IIa	
Objectives: The study was conducted to identify an individually well-tolerated dose associated with a statistically significant and clinically meaningful effect on postprandial blood glucose. The primary objective of the study was to assess the effects of individually increasing once-daily (QD) or twice-daily (BID) doses of AVE0010 in a stepwise manner on the increase in blood glucose induced by a standardized breakfast test meal. The secondary objectives were to assess the pharmacodynamics (PD), pharmacokinetics (PK), safety and tolerability after ascending doses of AVE0010, and to investigate the possible formation of antibodies against AVE0010 in plasma.	
Methodology: This was a multicenter study with a randomized, placebo-controlled, double-blind, parallel-group design. Eligible subjects were randomly assigned to one of the following treatments: • QD regimen: AVE0010 in the morning, placebo in the evening; • BID regimen: AVE0010 in the morning and evening; • Placebo-treatment: placebo in the morning and evening. The starting dose was 5 µg AVE0010 per subcutaneous (s.c.) injection (administered either QD or BID). If safety and tolerability permitted, the dose per injection was then to be increased every 5th day in increments of 2.5 µg. Dosing per injection was planned to be as follows: • Day 1 – Day 4: 5.0 µg • Day 5 – Day 8: 7.5 µg • Day 9 – Day 12: 10.0 µg • Day 13 – Day 16: 12.5 µg • Day 17 – Day 20: 15.0 µg • Day 21 – Day 24: 17.5 µg • Day 25 – Day 28: 20.0 µg	
The maximum treatment period was not to exceed 28 days, with a theoretical maximum dose of 20 µg AVE0010 QD or BID.In case of dose-limiting adverse events, the subjects could continue at the current dose level, or continue with the preceding dose, or they could be discontinued from treatment with study medication. Decisions on the dose progression in each subject were made by the investigator, and were based upon evaluation of blinded safety and tolerability data. Subjects who discontinued after receiving any dose of study medication could be replaced at the discretion of the sponsor. Subjects discontinued from treatment with study medication due to adverse events considered as possibly related to study medication were not to be replaced.	

Number of subjects**:** 60 male and female subjects with stable type 2 diabetes mellitus (20 subjects per treatment group)

Inclusion criteria: Male and female subjects, ≥ 18 to ≤ 70 years of age, with stable (in previous 3 months) type 2 diabetes mellitus treated with up to 2 oral hypoglycemic agents (sulfonylurea, metformin).

Treatments: Each subject received an s.c. injection 15 minutes prior to the morning and evening meals. Subjects treated with placebo received placebo injections in the morning and evening; subjects treated with the QD regimen received AVE0010 in the morning and placebo in the evening; subjects treated with the BID regimen received AVE0010 in the morning and in the evening.

Treatment started with a dose of 5 µg AVE0010 (or matching volume of placebo solution), which was then up-titrated every 5th day in steps of 2.5 µg to a maximum of 20 µg or to the maximum tolerated dose (in the event of dose-limiting adverse events).

Anthropometric data:

- Body weight: at baseline, on the 4th day of each dose step, and at final examination;
- Skin thickness at injection site.

Pharmacokinetic data: 24-hour PK profiling on Day 4 (4th day of the 5-µg dose level), on Day 12 (4th day of the 10-µg dose level), and on Day 28 (4th day of the final dose level, intended to be 20-µg).

Pharmacodynamic data:

- Day –1, and 4th day of each dose level: blood glucose determinations before and after the 3 standardized test meals (breakfast, lunch, dinner);
- Day –1, Day 12 (4th day of the 10-µg dose level), and Day 28 (last dosing): serum insulin, C-peptide and glucagon, gastrointestinal hormones (gastrin and gastro-inhibitory peptide);
- Morning fasting blood glucose levels on the 3rd day of each dose level;
- Day –1, Day 12 (4th day of the 10-µg dose level), and Day 28 (last dosing): 13C-octanoic acid breath test after the standardized breakfast test meal to explore gastric emptying rate.

Safety data

- Adverse events;
- Standard hematology, clinical chemistry, and urinalysis parameters;
- Formation of antibodies against AVE0010;
- Physical examination;
- Blood pressure and pulse rate (after 5 minutes in supine position);
- 12-lead ECG;
- Local tolerability at the site of injection.

Statistical procedures

The primary analysis variable was the change from baseline in the blood glucose area under the curve (AUC)[0:14h-4:55h] on the 4th day of the highest individually well-tolerated dose. An analysis of covariance (ANCOVA) was performed to analyze differences in the primary variable between treatment groups. Descriptive statistics and graphs are presented where applicable. Similar analyses were done for other PD variables.

PK analysis variables were determined if possible and adequate, by non-compartmental analysis.

An analysis of variance (ANOVA) was performed, and descriptive statistics and graphs are presented where applicable.

Safety variables were summarized using descriptive statistics.

Interim analysis

No interim analysis was performed.

Summary:

Results - Study subjects and conduct:

A total of 64 subjects (placebo, 22; AVE0010 QD, 21; AVE0010 BID, 21) were randomized and treated with at least one dose of study medication. Only one of these subjects (in the AVE0010 QD group) discontinued from the study during the treatment period after being treated for 20 days, due to an adverse event of hypersensitivity.

The mean age was 53.9 years (range 36 to 68 years), 59.4% of subjects were male, and 34.4% of subjects were white, 48.4% were black, and 17.2% were multiracial. The mean time since diagnosis of diabetes was 7.0 years, and the mean age of subjects at the time of diagnosis was 47.2 years.

Results - Anthropometric data:

Baseline body weights were slightly higher in the AVE0010 QD group (mean = 89.4 kg) than in the placebo (83.8 kg) and AVE0010 BID (83.7 kg) groups. Overall there was a slight decrease in body weight during the study in each treatment group. The differences to placebo for changes in body weight relative to baseline were not statistically significant between any of the treatment groups at any of the treatment levels. Skin thickness was generally comparable across the treatment groups at baseline.

Results - Pharmacodynamics: Treatment differences compared to placebo at the highest well-tolerated dose for the primary and key secondary PD variables are summarized in the table below.

Table 1 - Magnitude of treatment differences vs. placebo at the highest well-tolerate dose (mITT population)

Variable	Treatment difference at highest well-tolerate dose vs. placebo (p-value)	
	AVE0010 QD (N=21)	AVE0010 BID (N=21)
Change from baseline to Day 4 in the postprandial blood glucose AUC (h.mg/dL) at:		
Breakfast (primary analysis variable)	-381.3 (<0.0001)	-362.9 (<0.0001)
Lunch	-277.5 (0.0004)	-256.1 (0.0011)
Dinner	-179.1 (0.0162)	-357.5 (<0.0001)
Change from baseline to Day 4 in fasting blood glucose (mg/dL)	-20.2 (0.1039)	-25.0 (0.0477)
Change from baseline to Day 4 in average 7-point blood glucose profile (mg/dL)	-47.8(0.0007)	-56.2 (0.0001)
Change from baseline to Day 29 in HbA1c (%)[1]	-0.550 (0.0184)	-0.550 (0.0169)
Change from baseline to Day 4 in the HOMA insulin sensitivity parameters ([µIU/mL]/[mmol/L]):		
Beta cell function	1.36 (0.1265)	1.30 (0.2278)
Insulin resistance	0.83 (0.1655)	0.82 (0.1492)

[1] Change at all doses on Day 29.

HOMA = homeostasis model assessment.

Highly significant differences to placebo were seen in the AVE0010 QD and BID groups for the change from baseline to Day 4 at the highest well-tolerated dose in the postprandial blood glucose AUC at breakfast. Furthermore, the differences to placebo for the change from baseline in the postprandial blood glucose AUC were all highly significant at all dose levels for the meals at which AVE0010 had been administered, i.e., at breakfast for the AVE0010 QD group, and at breakfast and dinner for the AVE0010 BID group. In addition, at lunch the differences to placebo for the change from baseline in the postprandial blood glucose AUC were all highly significant at all dose levels for the AVE0010 QD group, and in the AVE0010 BID group the differences to placebo were statistically significant for dose levels of 12.5 µg and higher. At dinner, the differences to placebo were statistically significant in the AVE0010 QD group at all dose levels apart from 5 and 10 µg. Thus AVE0010 caused a clear attenuation of the rise in blood glucose induced by standardized test meals at all doses up to 20 µg, which was the highest dose tested and was also the highest well-tolerated dose for most subjects.

Except for the homeostasis model assessment (HOMA) parameters, the differences to placebo were also statistically significant at the highest well-tolerated dose for the key secondary variables in the AVE0010 BID group, and for the average 7-point blood glucose profile and glycohemoglobin (HbA1c) in the AVE0010 QD group. Only the difference to placebo for fasting blood glucose on the 4th day of treatment at the highest well-tolerated dose in the AVE0010 QD group failed to achieve statistical significance, although the difference to placebo for fasting blood glucose on the 3rd day of treatment was statistically significant in this treatment group ($p = 0.0145$).

For body weight, the difference to placebo for change from baseline at the highest well-tolerated dose was not statistically significant for the QD or BID regimen, indicating that the blood glucose lowering effects observed with AVE0010 were not attributable to weight loss.

In almost all cases, the magnitude of the differences to placebo for these PD variables tended to be dose dependent in both the AVE0010 QD and BID groups.

For HbA1c, which is the most important prognostic parameter for blood glucose control, there was a clear linear relationship between values measured at baseline and on Day 29, and all subjects treated with AVE0010 achieved a decrease in HbA1c value during the study.

Even though the changes in the HOMA parameter beta cell function compared to placebo were not statistically significant, pronounced mean increases were recorded between baseline and the 4th day of treatment with AVE0010 QD (an increase of 57.34 [µIU/mL]/[mmol/L] at the highest well-tolerated dose) and BID (an increase of 63.74 [µIU/mL]/[mmol/L]), whereas values remained relatively unchanged after treatment with placebo (an increase of 14.87 [µIU/mL]/[mmol/L]), suggesting an improvement in the insulin secretory capacity of the beta cells. These results were supported by insulin and C-peptide data, especially in the AVE0010 BID group, which had the highest mean post-treatment changes in insulin and C-peptide values despite having had the lowest mean baseline fasting blood glucose values.

Other PD effects induced by AVE0010 were suppression of glucagon after test meals, and decreases in the gastric emptying rate. Analytical difficulties preventing any meaningful data from being obtained for the gastrointestinal hormones (gastrin and gastro-inhibitory peptide).

Results - Pharmacokinetics: Antibodies against AVE0010 were detected in the plasma samples from Day 29 and the final visit in approximately 50% of subjects in the QD and BID dosing regimens. Because the presence of antibodies distorts the measurement of AVE0010 in plasma samples, separate PK analyses were performed for subjects who were antibody-positive or antibody-negative at Day 29. There were no differences in plasma PK for these two groups of subjects for the Day 4 and Day 12 analyses (all subjects were antibody-negative on Day 14). The focus of PK analyses was for subjects who were antibody negative on Day 29.

At steady state, plasma concentrations of AVE0010 increased in proportion to the dose administered (5 µg, 10 µg and 20 µg). For each dose level, morning concentration-time profiles were comparable in the QD and BID groups, and the evening profile for the BID group was comparable to the corresponding morning profile.

Mean AUC[0:14h-23:55h] and maximum concentration (Cmax) values generally increased in proportion to dose and dosing frequency. In the BID group, the mean AUC[0:14h-9:55h] value was comparable to the mean AUC[9:55h-23:55h] at the 5 and 10 µg dose levels, but at the 20 µg dose level the AUC[9:55h-23:55h] value was slightly higher than the AUC[0:14h-9:55h] value. For the 5 µg and 10 µg dose levels, median time to maximum concentration (tmax) [0:14h-9:55h] values were slightly longer in the BID group (1.75 h) than the QD group (1.25 h). This was also true for median tmax[0:14h-23:55h] values, where the difference between the BID group (2.25 h) and the QD group (1.25 h) was even greater. For the 20 µg dose level, median tmax values were the same for the QD and BID groups, for both measurement intervals (1.25 h).

The mean clearance of AVE0010 at steady state (CL/F[0:14-23:55h],ss) ranged between 21.2 and 28.5 L/h across treatment groups and dose levels, and was independent of the treatment group and dose level.

Median elimination half-lives ranged from 2.2 to 4.3 hours across treatment groups and dose levels.

Mean peak-to-trough fluctuation (PTF)[0:14h-23:55h] and PTF[0:14h-9:55h] values increased with each successive dose level. In the BID group, PTF[0:14h-9:55h] and PTF[9:55h-23:55h] values were comparable at the 5 µg dose level, but PTF[9:55h-23:55h]values were greater than PTF[0:14h-9:55h] values at the 10 and 20 µg dose levels.

Results - Pharmacokinetic-pharmacodynamic relationships: The relationship between the change in blood glucose AUC[0:14h-4:55h] and AVE0010 AUC[0:14h-9:55h] was investigated in subjects who were antibody-negative at Day 29. Comparison of QD and BID regimens showed no difference for AVE0010 AUC[0:14h-9:55h] and blood glucose AUC[0:14h-4:55h] between these regimens. No exposure-dependent influence on this PD parameter was observed.

Results - Safety: Treatment-emergent adverse events (TEAEs) were more frequent in subjects treated with AVE0010 (73.8% of subjects) than in subjects treated with placebo (50.0%), with comparable frequencies in the AVE0010 QD (76.2%) and BID (71.4%) groups. The highest frequencies of TEAEs in subjects treated with AVE0010 were for headache (24%), hypoglycaemia (12%), nausea (12%), diarrhoea (10%), upper respiratory tract infection (10%), dizziness (7%), and flatulence (7%). Headache and hypoglycaemia were more frequent in the AVE0010 groups than in the placebo group, and diarrhea and flatulence did not occur in the placebo group. Of note, diarrhea occurred only in the AVE0010 QD group, and there was no clear indication that nausea or vomiting were more frequent in either of the AVE0010 groups compared to placebo. Immune system disorders (all events were coded as hypersensitivity) were evenly distributed between the placebo and AVE0010 groups (one case in each group). One subject discontinued study medication due to a systemic allergic reaction (generalized urticaria with itching and hives) on Day 20 while being treated with AVE0010 15 µg QD, but this subject tested negative for AVE0010 antibodies. The remaining 2 cases of hypersensitivity were considered to have been allergies induced by food intake.

Although 57% of subjects in the AVE0010 QD and BID groups developed AVE0010 antibodies during the study, compared with no subjects in the placebo group, there were no adverse effects of these antibodies during the study in terms of immune system disorders.

Hypoglycemia was more frequent in the AVE0010 groups (AVE0010 QD: 2 subjects; AVE0010 BID: 3 subjects) than in the placebo group (1 subject), although the overall number of cases of hypoglycemia can still be considered as low. No subjects had hypoglycemia TEAEs leading to discontinuation of study medication.

There were no serious adverse events.

The frequency of injection site reactions was higher in the morning than in the evening, but at both timepoints the frequency of subjects with injection site reactions was comparable in the placebo and AVE0010 QD groups, and slightly lower in the AVE0010 BID group. The most frequently reported injection site reaction in each treatment group was erythema. All injection site reactions were mild, and there were no superficial observations such as erosion, dryness, scaling, cracking, crazing, scabbing, or glazing in any subjects. Thus the administration of AVE0010 was also well tolerated locally.

There were also no signals of concern revealed by the data for clinical laboratory tests, vital signs, ECG, or physical examinations. Thus the safety data in this study show that AVE0010 was safe and well tolerated, systemically and locally.

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