SYNOPSIS

Title of the study: A randomized, double-blind, parallel-group, placebo-controlled, ezetimibe-calibrated, multicenter study evaluating the safety and efficacy of four doses and two dose-regimens of AVE5530 over 4 weeks in patients with mild to moderate primary hypercholesterolemia

Investigator: [redacted]

Study centers: The study involved 28 sites in 6 countries: 5 sites in Chile, 5 in Hungary, 5 in Mexico, 5 in Russia, 4 in South Korea, and 4 in Turkey

Publications: Not applicable

Study period:

Date first patient treated: 14 March 2007

Date last patient completed: 26 October 2007

Phase of development: 2b

Objectives:

The primary objective of this study was:

- To assess the effect of AVE5530 on low-density lipoprotein cholesterol (LDL-C) levels over a period of 4 weeks in patients with mild to moderate hypercholesterolemia

The secondary objectives of this study were:

- To assess the effects of AVE5530 on other lipid plasma levels (eg, total cholesterol [Total-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, apolipoprotein-A1 [Apo-A1], apolipoprotein-A2 [Apo-A2] and apolipoprotein-B [Apo-B]) over a period of 4 weeks
- To assess the effects of administration of AVE5530 25 mg at dinner on LDL-C and other lipid levels over a period of 4 weeks
- To assess the safety and tolerability of AVE5530 over a period of 4 weeks

Methodology:

The study was comprised of 4 periods:

- A screening phase of 2 weeks on controlled (National Cholesterol Education Program Step I) diet
- A placebo single-blind lead-in period of at least 4 weeks. During the placebo lead-in phase, blood samples were collected at 3 occasions to assess for qualifying LDL-C levels
- A randomized, double-blind, parallel-group, fixed-dose of 4 doses and 2 dose-regimens of AVE5530, placebo-controlled and ezetimibe-calibrated period of 4 weeks of treatment, and
- A follow-up period of 3 days after the end of treatment

A double-blind design was used where patients received 5 identical capsules of treatment every day, 4 with breakfast and 1 at dinner

Number of patients: Screened: 509 Entered lead-in phase: 282 Randomized: 206 Completed: 200

Evaluated: Efficacy (intent-to-treat): 202 Safety: 206 Pharmacokinetics: 155

Diagnosis and criteria for inclusion: Male patients aged ≥18 years and postmenopausal women who signed informed consent and had mild to moderate primary hypercholesterolemia with LDL-C baseline ≥130 mg/dL and ≤250 mg/dL (≥3.36 mmol/L and ≤6.46 mmol/L), triglycerides ≤300 mg/dL (3.39 mmol/L), no lipid lowering drugs for at least 4 weeks at screening, and no Type I diabetes were included in the study

Investigational product: AVE5530

Dose: 5 mg, 25 mg, 50 mg, or 100 mg once daily in the morning and 25 mg once daily in the evening

Administration: Capsules at 5 mg or 25 mg administered orally just before or with breakfast and just before or with dinner

Batch numbers: Not disclosed

Duration of treatment: 8 weeks (4 week single-blind placebo lead-in and 4 week double-blind randomized treatment period)

Duration of observation: 10.5 weeks (73 days including 2-week screening, 4-week lead-in, 4-week randomized treatment, and 3 days follow-up period)

Reference therapy: Placebo

Dose: Not applicable

Administration: Capsules identical to AVE5530 5 mg or 25 mg administered orally just before or with breakfast and just before or with dinner

Batch numbers: [redacted]

Other therapy: Ezetimibe (calibrator)

Dose: 10 mg

Administration : Encapsulated tablets administered orally

Batch numbers: [redacted]

Criteria for evaluation:

Efficacy:

Primary efficacy criterion:

- Percent change in LDL-C from baseline to 4 weeks

Secondary efficacy criteria:

- Change in LDL-C levels from baseline to 4 weeks
- Percent change in other lipids (Total-C, triglycerides, HDL-C,) and lipoprotein fractions (Apo-B, Apo-A1, Apo-A2, and Apo-B/Apo-A1) from baseline to 4 weeks

Safety: Physical examination, vital signs, adverse events, hematology, and serum chemistry including liver tests and creatine phosphokinase.

Pharmacokinetics: The following AVE5530 plasma concentration data was determined: $C_{predose}$ (Day 1); C_{trough} (Day 14, Day 28); C_{2h} (Day 1, Day 14, Day 28); $C_{Follow\text{-}Up}$ (Day 31) and C_{1h}, C_{3h}, C_{4h}, C_{6h} (Day 28). The following primary pharmacokinetic variables were calculated for Day 28 using standard noncompartmental techniques: $AUC_{0\text{-}24h}$, AUC_{last}, C_{max}, T_{max}.

Pharmacokinetic sampling times and bioanalytical methods: AVE5530 blood samples were collected before and 2 hours after the first morning dose on Day 1, before and 2 hours after the morning dose on Day 14, before and 1, 2, 3, 4, 6 hours after the morning dose on Day 28 and during the follow-up visit on Day 31. AVE5530 plasma concentrations were assayed using liquid chromatography-tandem mass spectrometry with a lower limit of quantification (LLOQ) of 0.1 ng/mL.

Statistical methods:

Population for analyses:

- For the efficacy analyses, the primary population was the intent-to-treat population defined as all randomized and treated patients, with at least one on-treatment evaluation and a baseline evaluation for at least one of these criteria: LDL-C, HDL-C, Total-C, and triglycerides
- For safety analyses, a safety evaluable population was used which included all randomized and exposed patients who received at least one dose of double-blind study treatment. In the safety population, patients were considered in the group of treatment they received (as treated)

Statistical methods:

- The primary endpoint was the percent change from baseline in LDL-C levels at Week 4 or endpoint. Percent change in LDL-C was analyzed within the framework of an analysis of covariance (ANCOVA) model. The ANCOVA model included treatment as fixed factor (7 levels: 5 mg, 25 mg, 50 mg or 100 mg breakfast, 25 mg dinner of AVE5530 or placebo or ezetimibe) and baseline value as covariate. The dose effect relationship was tested through a closed, hierarchical testing procedure consisting of successive conditional trend tests and included only the 4 breakfast doses and the placebo
- In order to maintain an overall Type I error rate of 5%, a closed, hierarchical testing procedure was used to account for multiple testing
- Comparisons of 25 mg evening versus placebo and 25 mg morning versus 25 mg evening were performed as secondary analyses
- For efficacy criteria, 95% confidence intervals of the differences between each dose of AVE5530 and placebo as well as ezetimibe and placebo were provided
- Pharmacokinetics: Descriptive statistics of AVE5530 plasma concentration data and AVE5530 pharmacokinetic variables by treatment group were provided

Summary:

Efficacy results:

The AVE5530 25 mg, 50 mg, and 100 mg morning, and the 25 mg evening doses significantly reduced LDL-C levels over a period of 4 weeks in patients with mild to moderate hypercholesterolemia compared with placebo by –10.36% (p = 0.0019), –12.20% (p = 0.0002), –1.96% (p = 0.0001), and –14.53% (p = <0.0001), respectively. There was no difference between the AVE5530 5 mg morning dose and placebo. The observed mean difference between the 25 mg morning and 25 mg evening groups (-4.169%, p = 0.2160) showed a trend towards a larger effect with the evening dosing but the difference was not statistically significant.

Similar and parallel results were observed for Total-C, Apo-B, and Apo-B/Apo-A1. For other lipid parameters, HDL-C, triglycerides, and Apo- (A1, A2), no trends or changes versus placebo were evidenced for the AVE5530 morning or evening dose groups, or the ezetimibe group over a period of 4 weeks. Of note, in the hypertriglyceridemic patient subgroup, there was a significant difference in mean percent change in triglycerides from baseline to Week 4 in the 25 mg evening group compared to placebo (–27%, p = 0.0103).

Safety results:

Patients in this study had a mean exposure of 27 to 29 days across treatment groups. The overall incidence of treatment-emergent adverse events ranged from 10% (3 of 30 patients) in the placebo group to 34.6% (9 of 26 patients) in the AVE5530 100 mg morning group without a clear dose relationship. Only 2 individual preferred terms were reported in >1 patient: diarrhea and upper abdominal pain (2 patients each).

There were no deaths or reported serious treatment-emergent adverse events during the study. Two patients were discontinued from the study treatment due to adverse events, 1 from the AVE5530 25 mg evening group related to increases in transaminases due to alcohol intake, and 1 from the AVE5530 100 mg morning group due to atrial fibrillation related to the patient's history of hypertension and atherosclerosis.

In a few patients, postbaseline potentially clinically significant adverse events (PCSAs) were reported relating to clinical chemistry, hematology, vital signs, and electrocardiogram parameters with no relationship to study medication treatment. Treatment-emergent adverse events were reported in 3 patients with liver parameter PCSAs, 1 related to increases in alanine aminotransferase (ALT)/aspartate aminotransferase (AST)/gamma-glutamyl transferase (GGT) (due to alcohol consumption), 1 to viral hepatitis (and increases in ALT/AST/GGT/ alkaline phosphatase [ALP]), and 1 to increases in creatine phosphokinase not associated with myalgia (due to strenuous physical activity).

The Investigator considered these events not related to the study medication. In 1 patient with a PCSA for hematocrit, a treatment-emergent adverse event was reported related to a decreased red blood cell count. There were 3 PCSAs related to QTc prolongation, one of which was reported as a treatment-emergent adverse event. The Investigator considered none of these events as clinically significant.

Pharmacokinetic results:

Following the 4-week repeated oral administrations of 5 mg, 25 mg, 50 mg, or 100 mg AVE5530 once daily doses in patients with primary hypercholesterolemia, pharmacokinetic analysis showed low systemic AVE5530 exposure.

For 7 of 14, 6 of 18, 2 of 13, and 1 of 16 patients at 5 mg, 25 mg, 50 mg, and 100 mg AVE5530, respectively, all AVE5530 plasma concentrations were below LLOQ (0.1 ng/mL).

For all patients, individual AVE5530 plasma concentrations were below 1 ng/mL. With increasing AVE5530 doses, the exposure increased in a less than dose proportional manner. There was no indication of accumulation of AVE5530.

Conclusions: [redacted]

Date of report: 01-Aug-2008