SYNOPSIS

Title of the study: A double-blind placebo-controlled study of the activity of AVE1625 at doses of 10 mg and 40mg for 12 weeks in patients with mild to moderate Alzheimer's Disease

Study centers: Twenty-nine centers in 5 countries: France (1 center), Italy (7 centers), Netherlands (2 centers), Sweden (3 centers), United States (16 centers). There was no principal or coordinating Investigator.

Publications reference: None

Study period:

Date first patient enrolled: 06/Sep/2006

Date last patient completed: 12/Jul/2007

Phase of development: 2a

Objectives:

Primary

To assess the activity of AVE1625 at the doses of 10 and 40 mg/day in comparison to placebo in patients with mild to moderate Alzheimer's disease (AD):

- Safety and tolerability by monitoring of adverse events, clinical laboratories, and electrocardiogram (ECG)
- Efficacy by evaluation of cognitive, global, and behavioral parameters

Secondary

- To evaluate the pharmacokinetic parameters of AVE1625 in patients with mild to moderate AD

Methodology: Multi-center, multi-national, placebo-controlled, randomized, double-blind, parallel-group (3 groups)

Number of patients: Planned: 150; Randomized: 162 ; Treated: 162; Efficacy: 156; Safety : 162; Pharmacokinetics : 156 (including 52 placebo)

Diagnosis and criteria for inclusion: The diagnosis of AD was based on the DAT DSM-IV criteria and the NINCDS/ADRDA criteria for probable AD; supported by a modified Hachinski score < 4 and a computed tomography (CT) scan/ MRI of the brain performed within 12 months prior to randomization. If a patient was followed at the investigational center, had a previous CT scan / MRI scan (older than months) and had no focal clinical changes, new imaging was not necessary. The range of AD severity (mild to moderate) was established at screening by a Mini-Mental State Examination (MMSE) score ≥ 12 and ≤ 26.

Investigational product: AVE1625

Dose: 10 mg soft gelatin capsules (size 6, oblong, translucent) x 4 OD (for 40 mg/day), x 1 (+ 3 placebo) OD for 10 mg/day

Administration: Oral

Batch numbers: [redacted]

Duration of treatment: 12 weeks

Duration of observation: 18 to 24 weeks including screening period (up to 4 weeks), treatment period (12 weeks) and follow-up (6-8 weeks)

Reference therapy: Placebo

Dose: 0 mg soft gelatin capsules (size 6, oblong, translucent) x 4 OD

Administration: Oral

Batch number: [redacted]

Criteria for evaluation: The current report is an abbreviated report, and as such, only the safety results are being presented in full. The following safety criteria were evaluated and analyzed using descriptive statistics: Physical examination, adverse events (AEs), clinical laboratories including measurement of prothrombin time (PT)/international normalized ratio (INR), neurological assessment, vital signs and ECG. Efficacy had been evaluated at baseline, 8 and 12 weeks, by using Alzheimer's Disease Assessment Scale – Cognitive subscale, Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change scale and MMSE. Other efficacy endpoints; the Neuropsychiatric Inventory scale (NPI) total score (frequency x severity) and Alzheimer's disease cooperative study – activities of daily living inventory scale, were measured at baseline and week 12.

Statistical methods: Summary of treatment-emergent adverse events (TEAEs) was based on the Medical Dictionary for Regulatory Activities coding of verbatim terms reported by investigators. TEAEs were defined as any AEs newly developed or worsened or became serious on or after the day of first dose intake of study drug, up to the day of end of study. Although every effort was made to establish the onset date and time, events with missing onset date were considered as TEAEs. For selected laboratory tests, vital signs and ECG, incidences of potentially clinically significant abnormality values were summarized. QTc interval was assessed using both Fridericia's method (QTcF) and Bazett's method (QTcB).

Summary:

A similar number of patients were randomized into each arm. The age, race, country and duration of disease were similar in all groups. However, while the male/female ratio was approximately 1:1 in the 10 mg and 40 mg treatment groups, the proportion female patients in the placebo group was higher (7:3). This potentially drove an imbalance between the placebo group and each of the treatment groups in weight. The patients in the 2 active treatment groups had similar disease severity which was slightly milder than in the placebo group. The exposure to the study drug and the compliance to the investigational product was similar in all treatment groups.

Efficacy results/conclusions:

A benefit of treatment was not shown in the efficacy variables of cognition, global assessment, activities of daily living or psychiatric symptoms with either dose. For the psychiatric symptoms measured by the NPI, the high dose (40 mg) group had poorer performance compared to placebo, and there was a trend for poorer performance in the low dose (10 mg) group.

Safety results/conclusions:

The rate of premature discontinuation from treatment was higher in the 40 mg treatment group than in placebo. This higher rate was also seen in the 10 mg group but to a lesser degree. In the treated groups, the main reasons for discontinuation was gastro-intestinal disorders (nausea/vomiting) and psychiatric disorders (agitation, hallucination).

There were two deaths (one cerebrovascular accident and one sudden death, suspected myocardial infarction). Both subjects who died were in the 40 mg treatment group.

The more frequent TEAEs were gastrointestinal (nausea, vomiting), psychiatric (mainly agitation), general (asthenia, fatigue), nutrition (anorexia), nervous system (dizziness) disorders and occurred more commonly in the 40 mg treatment group compared to placebo. Most of them were also seen in the 10 mg group but to a lesser extent than the 40 mg group. More skin disorders (pruritus/erythema) were observed in the 40mg treatment group. Rash was observed in both the 10 and 40 mg treatment groups. Various pain AEs (backpain, arthralgia, pain in extremity) were observed only in treated groups. Few more cardiac events were observed in treated groups, without apparent common physiopathology.

Weight loss demonstrated by a change in the mean weights and the rate of weight loss ≥ 5% was higher in the 40 mg treatment group compared to placebo. This weight loss was also seen in the 10 mg treatment group although to a lesser degree.

No significant changes in ECG and clinical laboratory parameters were identified, including CPK, liver enzymes and PT/INR.

Date of report: 17-Oct-2008