SYNOPSIS

Title of the study: A double-blind, randomized, placebo-controlled, study of the safety and activity of four escalating single doses of AVE0657 in patients suffering from Obstructive Sleep Apnea Hypopnea Syndrome (ACT6796)
Coordinating Investigator: [redacted]
Study centers: Six centers in 3 countries in Europe: France (3 centers), Germany (2 centers) and Spain (1 center)
Publications (reference): None
Study period: Date first patient enrolled: 28/Jan/2008 Date last patient completed: 19/Jan/2009
Phase of development: Phase 2a
Objectives: ***Primary*** To demonstrate the effect of AVE0657 on the Apnea Hypopnea Index (AHI) after a single dose administration in patients with Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) ***Secondary*** To evaluate the clinical and biological safety and tolerability of AVE0657 in a population of patients with OSAHS To evaluate pharmacokinetic parameters in this population To evaluate the effect of AVE0657 on additional polysomnographic measurements in this population
Methodology: Phase 2, multi-center, randomized, double-blind, placebo-controlled study with 4 groups of dose escalation
Number of patients: Planned: 36 (5-6 per center); Randomized: 38; Treated/safety: 38, Efficacy: 37; Pharmacokinetics: 36
Diagnosis and criteria for inclusion: Patients aged 18 to 75 years, diagnosed with Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS): Diagnostic and Coding Manual 2005 with an AHI ≥15 and up to 35 including ≥60% obstructive or mixed AH-Daytime sleepiness or at least 2 of the following: choking/gasping during sleep, recurrent awakenings from sleep, daytime fatigue, unrefreshing sleep, impaired concentration along with irritability or mood swings

Investigational product: AVE0657

Dose: **Number of capsules used per blister / dose group**

Dose (mg)	Number of capsules			Total
	20 mg	100 mg	Placebo	
40	2	0	2	4
100	0	1	3	4
160	3	1	0	4
320	1	3	0	4

Administration: Each randomized patient was administered orally (approximately 30 minutes prior to subject lying down to sleep) 4 capsules per dose group in 1 single intake, as described in the table above.

Duration of treatment: 1 day (Single dose)

Duration of observation: 5-7 days

Reference therapy: Placebo of AVE0657 capsules

Dose: 0 mg

Administration: Oral

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; Adverse events (AEs), vital signs, clinical laboratory (biochemistry, hematology, coagulation, urinalysis), respiratory parameters (respiratory rate, arterial blood gas, Borg dyspnea self-rating scale) and ECG data. Borg dyspnea self-rating scale (a non linear scale: from 0 [no breathlessness] to 10 [maximum]) was used to measure dyspnea after awaking.

The main efficacy criteria was the change from baseline to post treatment in apnea hypopnea index (AHI).

Statistical methods: The safety population was defined as all patients who were exposed to study medication. For safety parameters, patients were analyzed in the treatment group they actually received. Summary of treatment-emergent adverse events (TEAEs) was based on the Medical Dictionary for Regulatory Activities (MedDRA) coding of verbatim terms reported by Investigators. TEAEs were defined as AEs that developed, worsened or became serious from the first dose of study medication to 2 days (48 hours) after the last drug intake. Although every effort was made to establish the onset date and time, events with incomplete or missing onset dates were considered as TEAEs except the incomplete date (eg, month and year) clearly indicated that the event started prior to treatment or post treatment. For selected laboratory tests, vital signs and electrocardiogram (ECG centralized automatic and manual readings), incidences of potentially clinically significant abnormality (PCSA) or out-of range values were summarized. QTc interval was assessed using both Fridericia's (QTcF) and Bazett's (QTcB) methods.
Efficacy analyses were preformed using the intent-to-treat (ITT) population, defined as all treated patients with a baseline and post baseline AHI. Patients were analyzed in the treatment group they actually received. The main efficacy analysis was a trend test of dose-response relationship using a linear regression adjusted on baseline AHI. In addition, the effect of each dose of AVE0657 as compared to placebo was estimated using an analysis of covariance (ANCOVA) and a series of sensitivity analyses were conducted.

Summary:

A total of 38 patients were randomized, among which 2 withdrew (1 in the placebo group, 1 in AVE0657 320 mg group) before receiving treatment. Two patients not properly randomized through the Interactive Voice Recognition System (IVRS), were treated by the Investigator in a blinded fashion. Out of the 38 patients that were treated (safety population), 14 were in the placebo group and 6 in each of the 4 AVE0657 dose groups (40, 100, 160 and 320mg). Age ranged from 34 to 73 years, while the BMI was 21 to 34 kg/m^2. The male/female ratio was 2:1 in the 40 mg and 100 mg treatment groups, 6:1 in the placebo treatment group and 6:0 in the 160 mg and 320 mg treatment groups. Thirty-five out of 38 (92.1%) patients were Caucasians, 2 were Asian, Oriental, and 1 was of 'Other' origin (half European, half Arabic). Eleven patients out of 38 (28.9%) were of Hispanic origin and 24/38 (63.2%) had a smoking history.

Efficacy results:

A benefit of treatment was not shown on AHI, the primary efficacy endpoint, whatever the analysis (results did not indicate differences between placebo and treated groups). The analysis of obstructive apnea hypopnea index (OAHI), the key secondary endpoint, resulted in similar conclusions. There was no change after treatment in the other secondary endpoints, which included other polysomnogram (PSG) parameters: index of micro arousals, central apnea hypopnea index (CAHI), time spent with oxygen partial saturation and average oxygen partial saturation (%).

Safety results:

No patient discontinued the study for adverse event and there were no SAEs or deaths reported. The percentage of patients experiencing TEAEs for each AVE0657 dose level was higher than placebo: 16.7% for AVE0657 100 mg, 33.3% for 40 and 160 mg, respectively, and 50% for 300 mg versus 7.1% for placebo. No apparent dose-relationship and no particular pattern was observed for TEAEs. The most frequently reported TEAEs in AVE0657 patients, by body system organ class (SOC), were in the eye disorder and nervous system disorder. All TEAEs were mild to moderate in intensity and considered by the Investigator as possibly related to the study drug except visual impairment in AVE0657 160 mg group, vision blurred and postprocedural hematoma in AVE0657 320 mg group. No TEAE was reported in more than 1 patient except headache, reported in 2 patients. One patient in the 320 mg group who had a high creatine phosphokinase (CPK) value (467 UI/L, >3ULN) at entry in the study, had a TEAE of atypical muscular pain (myalgia), which resolved after corrective treatment (piroxicam). All patients, except 2 (1 elderly patient in the AVE0657 160 mg group having polyuria and 1 patient in the AVE0657 320 mg group having headache) had recovered from all TEAEs.

Most of the patients were rated 2/10 (Slight breathlessness) or less at baseline on dyspnea as assessed by Borg scale. Only one patient had a change from baseline to posttreatment (from the 320mg dose, 1-point improvement). There was no safety signal on laboratory (including renal and liver functions), ECG, and vital signs. There was no relevant change in arterial blood gases parameters (PaO2 and PaCO2).

Date of report: 29-Jun-2009