SYNOPSIS

Title of the study: A double-blind, randomized, placebo-controlled, study evaluating the safety and activity of four escalating single doses of AVE0657 in congestive heart failure patients presenting as Cheyne-Stokes Breathing Syndrome (CSBS) – (ACT6795 study)
Coordinating Investigator: [redacted]
Study centers: Three centers in 2 countries in Europe: France (2 centers) and Germany (1 center)
Publications (reference): None
Study period: Date first patient enrolled: 27/May/2008 Date last patient completed: 30/Mar/2009
Phase of development: Phase 2a
Objectives: ***Primary*** The primary objective of this study is to demonstrate the effect of AVE0657 on the Apnea Hypopnea Index (AHI) after a single dose administration in patients with Cheyne-Stokes Breathing Syndrome (CSBS) ***Secondary*** To evaluate the clinical and biological safety and tolerability of AVE0657 in a population of patients with CSBS To evaluate pharmacokinetic parameters in this population To evaluate the effect of AVE0657 on additional polysomnographic measurements in patients with CSBS
Methodology: Phase 2, multi-center, randomized, double-blind, placebo-controlled study with 4 groups of dose escalation
Number of patients: Even though 36 patients were initially planned in 4 cohorts (AVE0657 40, 100, 160 and 320 mg) with 9 patients per treatment group (6 AVE0657, 3 placebo), only 13 were screened in the first cohort (AVE0657 40 mg) and 8 (6 AVE0657, 2 placebo) out of 13 randomized due to the premature termination of the study by the Sponsor for development strategy. All 8 patients were treated and analyzed for efficacy, safety and pharmacokinetics.
Diagnosis and criteria for inclusion: Male and female out-patients ≥18 years old, presence of congestive heart failure (CHF) assessed by history of echocardiography data and New York Heart Association (NYHA) class II-III and of typical cyclic crescendo and decrescendo change in breathing amplitude AHI ≥10 and <60 and majority of the apneas to be ≥60% central in origin.

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 of the 8 patients randomized was administered orally (approximately 30 minutes prior to subject lying down to sleep) 4 capsules (AVE0657 20 mg or placebo) in 1 single intake as described in the table above. The 3 other cohorts were not used due to early termination of the study (see explanation above).

Batch number: FRA-00863 for the 20 mg capsules

Duration of treatment: 1 day (Single dose)

Duration of observation: 5-7 days

Reference therapy: Placebo of AVE0657 capsules

Dose: 0 mg

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: 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 variable was the change from baseline to post treatment in apnea hypopnea index (AHI, [number/hour]). The key secondary efficacy variable was the change from baseline to post-treatment in Central Apnea Hypopnea Index (CAHI, [number/hour]). CAHI is the central component of 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. Due to early termination of the study, the dose-response test was not performed. Efficacy parameters were only summarized using descriptive statistics.

Summary:

A total of 13 patients were screened in cohort 1 (AVE0657 40 mg) of which 8 were randomized: 2 in the placebo group and 6 in the AVE0657 40 mg dose group. All patients were Caucasian males aged 46 to 76 years old while the BMI was 21 to 30 kg/m^2. Six out of 8 (75%) patients had a smoking history.

Efficacy results/conclusions:

Compare with placebo, the higher AHI decrease (change from baseline) was -29 in the treated group; observed in 1 patient who had not met inclusion criteria. A worsening of +6 was observed in 1 other patient who had an obstructive sleep apnea syndrome (SAS) based on central reading (baseline apneas or hypopneas were < 60 % and central in origin [AHI = 22.5 and CAHI = 6.4]). Two other patients in the treated group showed an improvement of central sleep apnea, however, they displayed obstructive sleep apnea during the treated night so that no overall change could be shown on their AHI value. For the other patients including those of the placebo group, the second nights were not associated with qualitative change of the sleep apnea such that changes observed in CAHI and AHI were consistent.

Overall, these observations were made on a small sample size due to early termination of the study as explained above. They did not allow commenting on potential therapeutic activity of the compound (for the primary or secondary endpoints) at the tested dose.

Safety results/conclusions:

No patient discontinued the study for adverse event and there were no SAEs or deaths reported. Only 1TEAE of mild transient back pain (musculoskeletal and connective tissue disorders body system organ class [SOC]) was reported in 1 patient in the treated group. The TEAE was not considered by the Investigator as related to the study drug and had resolved without corrective treatment.

All patients were rated 3/10 (moderate breathlessness) or less at baseline on dyspnea as assessed by Borg scale. Three patients had a change from baseline to posttreatment: 1 in the Placebo group with 1-point decrement, 2 in the AVE0657 40mg group with 1- and 2-points decrement, each, respectively.

There was no safety signal on laboratory (including renal and liver functions), ECG, vital signs and arterial blood gases parameters (PaO2 and PaCO2).

These observations made on a small sample size owing to the early termination of the study and to the fact that only the unique dose of AVE0657 40mg was tested, did not allow commenting on potential therapeutic activity and/or effects of the compound.

Date of report: 20-August-2009