SYNOPSIS

Title of the study: Comparison of the safety and efficacy of volinanserin and lormetazepam in the treatment of insomnia characterized by sleep maintenance difficulties. A 4 week, randomized, double-blind, double-dummy, comparative, parallel-group study (EFC10550)

Investigator(s): There was no coordinating Investigator in this study.

Study centers: 15 active (for screening) centers in 3 countries: 11 in France, 1 in Spain, and 3 in Sweden

Publications (reference): None

Study period:

Date first patient enrolled: 04 November 2008

Date last patient completed: 30 January 2009

Phase of development: Phase 3

Objectives:

Primary:

To compare the potential for next-day residual effects of volinanserin 2 mg/day and lormetazepam 1 mg/day by measuring the sleepiness in the morning using the patient's sleep questionnaire during 4 weeks of treatment in patients with chronic primary insomnia and sleep maintenance difficulties

Secondary:

- To compare the clinical safety of both products, including the potential for rebound insomnia and withdrawal symptoms after treatment discontinuation
- To compare the efficacy of both products on subjective sleep parameters (patient reported (pr)-Wake time After Sleep Onset (WASO), pr-Total Sleep Time (TST), pr-Number of Awakenings (NAW), pr-Sleep Onset Latency (SOL), Quality of Sleep (QoS), refreshing QoS)
- To compare the effects of both products on patient's daytime functioning using the Sleep Impact Scale (SIS) after 4 weeks of treatment

The study was stopped prematurely by the Sponsor after 33 patients were randomized. Therefore, the analysis (as defined in the statistical analysis plan) focused on a review of the safety profile based on the reported adverse events. Limited appendices are included to support the data presented in this synopsis-style clinical study report.

Methodology:

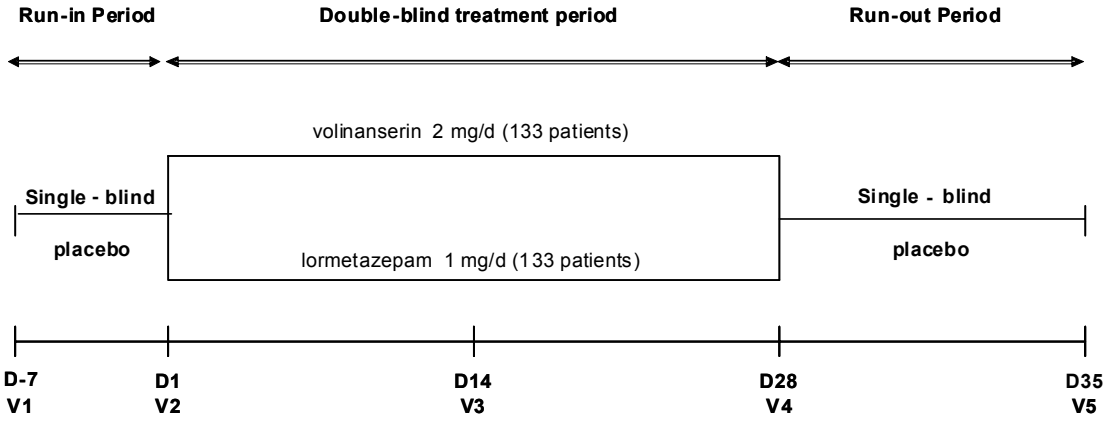
This was an international, multicenter, Phase 3, randomized, double-blind, double-dummy, comparative study with 2 parallel groups of patients with insomnia characterized by sleep maintenance difficulties.

After a placebo run-in period of 7 days, patients were to be centrally randomized using an interactive voice response system to receive either volinanserin 2 mg/day or lormetazepam 1mg/day in a 1:1 ratio The randomization was stratified by center. At the end of the 4-week double-blind treatment period, patients were to be followed for a placebo run-out period for approximately 7 days. Patients withdrawing prematurely from the treatment phase were to be followed for 7 days without placebo intake.

Patients received 1 tablet and 1 capsule during each study period: placebo tablet and capsule in the run-in and run-out periods and either volinanserin tablet with placebo capsule or lormetazepam capsule with placebo tablet during the double-blind treatment period.

An external Data Monitoring Committee periodically reviewed patient safety data.

A summary of the study design is provided below.



Number of patients: Planned: 266 (133 per treatment group) Randomized: 33 Treated: 33 Efficacy: Not applicable Safety: 33
Diagnosis and criteria for inclusion: Patients of either sex aged ≥ 18 years diagnosed with primary insomnia based on the criteria described in the Diagnostic and Statistical Manual of Mental Disorders 4th edition text version, with predominant complaints of difficulty in maintaining sleep for at least 1 month preceding the study visit and having clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Investigational product: volinanserin 2 mg tablets Dose: 2 mg/day Administration: oral, once daily immediately before bedtime Batch number: [redacted]
Duration of treatment: 4 weeks of double-blind treatment **Duration of observation:** 6 weeks, including a 1-week run-in period, 4 weeks of double-blind treatment, and a 1-week run-out period.
Reference therapy: placebo tablet (to match volinanserin) Dose: not applicable Administration: oral, once daily immediately before bedtime Batch number: [redacted]
Reference therapy: placebo capsule (to match lormetazepam) Dose: not applicable Administration: oral, once daily immediately before bedtime Batch number: [redacted]

Reference therapy (comparator): lormetazepam capsule

Dose: 1 mg

Administration: oral, once daily immediately before bedtime

Batch number: [redacted]

Criteria for evaluation:

The current report is a synopsis-style clinical study report; consequently, only safety results are presented. The safety analysis was based on the reported adverse events presented by system organ class and preferred term. Safety criteria were evaluated and analyzed using descriptive statistics.

Evaluation criteria as originally specified in the protocol are listed below.

Safety

Primary criterion: sleepiness in the morning measured on a visual analog scale of the patient's sleep questionnaire

Secondary criteria:

- Ability to concentrate, measured on a 4-category scale (excellent, good, fair, and poor) of the patient's sleep questionnaire
- Rebound effect measured daily during the run-out period by pr-WASO and pr-SOL on the patient's sleep questionnaire
- Withdrawal symptoms measured on the Physician's Withdrawal Checklist, assessed during the run-out period by change from Day 28 to Day 35 for each of the 20 symptoms and on total score
- Vital signs (supine and standing systolic and diastolic blood pressure: supine and standing heart rate, weight at all visits, height at baseline)
- Complete physical examination at Visits 1, 4, and 5
- Adverse event reporting at every visit
- Standard laboratory tests and 12-lead electrocardiogram at Visits 1 and 4

Efficacy

- Subjective sleep parameters measured on the patient's sleep questionnaire (pr-WASO, pr-TST, pr-NAW, pr-SOL, QoS, refreshing QoS)
- Patient's Global Impression and Clinical Global Impression of the Investigator at Visits 3, 4, and 5
- Daytime functioning (SIS) at Visits 2, 4, and 5

Statistical methods:

Based on the absence of a demonstration of efficacy in a recently completed Phase 3 study, the Sponsor decided to discontinue the volinanserin development program in sleep maintenance insomnia. Accordingly, this ongoing study was prematurely terminated with only 33 patients randomized. Analyses specified in the Statistical Analysis Plan focused on patient disposition, demography, and adverse events.

Demographic characteristics were summarized on the randomized population. Continuous data were summarized using the number of available data, mean, standard deviation, median, and minimum and maximum for each treatment group. Categorical and ordinal data were summarized using numbers and percentages of patients in each treatment group.

The safety analysis was performed on the all-treated population, defined as all randomized patients exposed to study treatment, regardless of the amount of treatment administered. Safety analyses focused on treatment-emergent adverse events (TEAEs), defined as events that developed, worsened, or became serious on or after the randomization date. Frequency distributions of TEAEs are provided by system organ class and preferred term and by system organ class, high level group term, high level term, and preferred term and include TEAEs leading to treatment discontinuation. Adverse events were coded before study unblinding using the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1.

No efficacy or pharmacogenetic analyses were performed.

Summary

Patient population: A summary table of the randomized and all-treated populations is provided below. The randomized population was identical to the all-treated population. A total of 50 patients were screened and 33 randomized.

Summary of populations - randomized population

	Volinanserin 2mg/day	Lormetazepam 1mg/day	All
Randomized population	17 (100%)	16 (100%)	33 (100%)
All treated population	17 (100%)	16 (100%)	33 (100%)

Note: % calculated using the number of randomized patients as denominator.

Patient disposition: All randomized patients were exposed to at least 1 dose of the investigational product or comparator. A total of 27 randomized patients completed the study treatment period as specified in the protocol; 6 patients discontinued study treatment. Three discontinuations were due to adverse events (headache, global amnesia, and cholecystectomy), of which 1 was a nontreatment-emergent adverse event, and 3 were due to termination of the study by the Sponsor.

Summary of patient disposition at end of double-blind treatment n (%) - randomized population

	Volinanserin 2mg/day (N=17)	Lormetazepam 1mg/day (N=16)
Exposed patients	17 (100%)	16 (100%)
Completed study treatment period	15 (88.2%)	12 (75.0%)
Discontinued study treatment period	2 (11.8%)	4 (25.0%)
Reason for treatment discontinuation		
Adverse event	1 (5.9%)	2 (12.5%)
Other reason	1 (5.9%)	2 (12.5%)

Note: % calculated using the number of randomized patients as denominator.

Demographics:

Summary of demographics characteristics at baseline - randomized population

	Volinanserin 2mg/day (N=17)	Lormetazepam 1mg/day (N=16)	All (N=33)
Gender, n(%)			
Number	17	16	33
Male	3 (17.6%)	3 (18.8%)	6 (18.2%)
Female	14 (82.4%)	13 (81.3%)	27 (81.8%)
Race, n(%)			
Number	17	16	33
Caucasian / white	17 (100%)	16 (100%)	33 (100%)
Age(years)			
Number	17	16	33
Mean (SD)	53.71 (13.38)	51.81 (10.88)	52.79 (12.08)
Median	56.00	53.00	54.00
Q1:Q3	41.00 : 63.00	42.50 : 58.00	42.00 : 63.00
Min : Max	32.0 : 73.0	34.0 : 72.0	32.0 : 73.0
Age Group, n(%)			
Number	17	16	33
[18-45[years	5 (29.4%)	5 (31.3%)	10 (30.3%)
[45-65[years	9 (52.9%)	9 (56.3%)	18 (54.5%)
>= 65 years	3 (17.6%)	2 (12.5%)	5 (15.2%)

Note: Number corresponds to the count of patients with non-missing data used for the calculation of the percentage.

Safety results

Summary of adverse events: Few TEAEs and no deaths or serious adverse events were reported during the study. Of the 3 patients who permanently discontinued treatment due to adverse events, 2 discontinuations were due to TEAEs (1 in each treatment group), and 1 was due to a nontreatment-emergent adverse event. There were no occurrences of the adverse events of special interest (diverticulitis or sigmoiditis) that were prespecified in the protocol. The safety profile is presented in the table below.

Brief summary of adverse events

	Volinanserin 2mg/day (N=17)	Lormetazepam 1mg/day (N=16)
Patients with any TEAE (including SAEs)	3 (17.6%)	4 (25.0%)
Patients with any serious TEAEs (including SAEs leading to death)	0	0
Deaths	0	0
Patients permanently discontinued treatment due to TEAE	1 (5.9%)	1 (6.3%)

Note: TEAE: Treatment-emergent adverse event. SAE: serious adverse event.
Adverse events coded in MedDRA version 11.1

Summary of treatment-emergent adverse events

See the following table for all TEAEs reported during the study by treatment group. No patterns of occurrence of TEAEs were observed. One subject in the volinanserin treatment group had an increase in creatine phosphokinase on Day 34; no corrective action was taken and she was recovering at the end of the study.

Number (%) of patients experiencing TEAEs by primary system organ class and preferred Term – all treated population

Primary system organ class by preferred term	Volinanserin 2mg/day (N=17)	Lormetazepam 1mg/day (N=16)
Any TEAE	3 (17.6%)	4 (25.0%)
Infections and infestations	1 (5.9%)	1 (6.3%)
Sinusitis	1 (5.9%)	0
Influenza	0	1 (6.3%)
Nervous system disorders	1 (5.9%)	1 (6.3%)
Global amnesia	1 (5.9%)	0
Transient ischaemic attack	1 (5.9%)	0
Sciatica	0	1 (6.3%)
Investigations	1 (5.9%)	0
Blood creatine phosphokinase increased	1 (5.9%)	0
Gastrointestinal disorders	0	1 (6.3%)
Vomiting	0	1 (6.3%)
Surgical and medical procedures	0	1 (6.3%)
Cholecystectomy	0	1 (6.3%)

Note: TEAE: Treatment emergent adverse event, SOC: system organ Class, PT: preferred term.
Primary SOC and PT sorted by decreasing frequency in volinanserin 2mg/day then in lormetazepam 1mg/day group.
Adverse events coded in MedDRA version 11.1

Treatment-emergent adverse events leading to discontinuation

Two TEAEs led to study drug discontinuation. A 68-year-old female patient receiving volinanserin 2 mg/day experienced severe global amnesia on Day 10 (1-day duration), and a 64-year-old female patient receiving lormetazepam 1 mg/day required a cholecystectomy on Day 12; she recovered in 2 days.

Conclusions: [redacted]

Date of report: 16-Jun-2009