This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2 Synopsis

Investigators:	4 investigators in Germany	
Clinical Trial Centres:	4 centres in Germany	
Publication:	Not yet published	
Studied Period (Years): Date of First Enrolment: Date of Last Completed:	 22.02.2007 10.12.2007	**Phase of Development:** Phase III trial
Sponsor's Responsible Person:	[redacted]	
Coordinating Investigator: (=Director of Clinical Investigation)	[redacted]	
Objectives:	The objective of this clinical trial was to evaluate the clinical efficacy and tolerability of frovatriptan in comparison with placebo for the prophylactic treatment of episodic cluster headache.	
Methodology:	This was a multi-centre, placebo-controlled, randomised, double-blind, prospective phase III parallel-group trial with two independent treatment groups to assess the effect of 5 mg frovatriptan given once daily on the frequency of cluster headache attacks as compared to placebo. The trial consisted of a run-in period (4 to 7 days), treatment period (14 days), and a follow-up period (7 days). Patients were randomly assigned to receive frovatriptan 5 mg or placebo in a 1:1 ratio after the run-in period (Visit 2).	
Premature termination:	The trial was prematurely discontinued after 11 patients had been enrolled due to infeasibility. Patient recruitment was slow and all patients enrolled presented with major protocol violations (mainly intake of prohibited previous and concomitant medication) not allowing for a meaningful analysis.	

No. of Patients:	Planned: 80 evaluable patients (40 per group) Analyzed: Safety: 11 pts (frovatrioptan N = 4, placebo N = 6) ITT: 10 pts (frovatrioptan N = 5, placebo N = 6) ITT = intention-to-treat, N = number of patients, pts = patients.
Diagnosis / Indication and Main Criteria for Inclusion:	Male and female patients between 18 and 65 years suffering from known episodic cluster headache (according to the diagnostic criteria of the IHS) were recruited. Further inclusion criteria were: - At least second episode of cluster headache. - Duration since onset of first attack of the current episode at least one week. - Expected duration of cluster episode at least 6 weeks after start of screening. - Response to oxygen inhalation (relevant change in headache severity). To be randomised patients had to further demonstrate an attack frequency between one attack every 2 days and 8 attacks per day at Visit 2.
Test Product, Dose, Mode of Administration, Batch-No.:	Allegro® Active ingredient: frovatriptan Pharmaceutical form: film-coated tablets Strength: 2.5 mg Daily dose: 5 mg, taken once daily Mode of administration: oral Batch-No.: C1006091 (corresponds to PDMS Batch No.: 045 and 61022 listed in the Certificates of Analysis)
Duration of Treatment for Each Patient:	14 days
Reference Therapy, Dose, Mode of Administration, Batch-No.:	Placebo Pharmaceutical form: film-coated tablets Mode of administration: oral Batch-No.: C1006091 (corresponds to Batch No.:FRO2006071 listed in the Certificates of Analysis)

Criteria for Evaluation: **<u>Efficacy:</u>**	*Primary variable:* Mean cluster headache attack frequency per week during the 2-week treatment period. *Secondary efficacy variables:* • Mean cluster headache attack frequency per week during the first week and second week of treatment period and the 1-week follow-up period. • Proportion of responders regarding the cluster headache attack frequency. • Mean maximum pain intensity of cluster headache attacks. • Mean and total duration of cluster headache attacks. • Associated autonomic symptom of cluster headache attack. • Oxygen use. • Use of additional drug treatment. • Quality of life (SF-36 questionnaire). • Global efficacy of the treatment. • Treatment satisfaction.
<u>Safety:</u>	• Adverse events (AE) • Laboratory variables • Vital signs • Physical examinations • Exercise electrocardiogram (ECG)/ ECG
Statistical Methods:	For the primary variable treatment groups were compared using the 2-sided exact Wilcoxon-Mann-Whitney test at a significance level of 5%. Secondary efficacy variables and safety were analysed by descriptive methods.

SUMMARY - CONCLUSIONS

Efficacy Results

Primary variable:
The mean cluster headache frequency per week during treatment was higher in the frovatriptan as compared to the placebo group (14.1 vs. 10.1). The difference was not statistically significant.

Secondary variables:
Regarding cluster headache attack frequency, there was one responder (25.0%) in the frovatriptan group and 4 responders (66.7%) in the placebo group.

The frequency of headache attacks per week continuously decreased over time with placebo but remained rather constant with frovatriptan (attack frequency during run-in, 1st treatment week, 2nd treatment week and follow-up in the frovatriptan group: 15, 14, 14, and 11; in the placebo group: 16, 12, 8, and 3).

Mean attack duration was shortened with frovatriptan (from 56 to 41 min) but not with placebo treatment.

With regard to quality of life, placebo-treated patients performed better than frovatriptan-treated patients for almost all scores.

For all other secondary variables no differences were apparent.

Safety Results

During the entire study, 3 AEs were reported by 3/5 frovatriptan-treated patients (60.0%) and 6 AEs were reported by 3/6 placebo-treated patients (50.0%). During the 14-day treatment period, there was no AE in the frovatriptan group; in the placebo group 6 AEs were reported by 3/6 patients (50.0%). For 4 of the 6 AEs reported during the treatment period in the placebo group the relationship to study medication was judged to be probable, possible, or certain (= adverse reaction). There was only one severe AE (conjuncitivits bacterial) which occurred during the run-in period.

No patient died during the study and no SAEs occurred during the study.
No clinically meaningful changes in hematology and serum chemistry parameters were found that would give rise to a safety concern related to treatment with frovatriptan. There were also no clinically meaningful changes in vital signs, ECGs and physical examination parameters.

Conclusion

With only 11 patients included who in addition all presented with major protocol deviations (mainly intake of prohibited medication to treat headache), the study was not powered to show significant differences between treatments and the results seen are most probably due to chance rather than to any treatment effect. No significant differences or trends were observed neither for the primary nor any secondary efficacy parameter. Substantial differences between treatment groups were seen in the body mass index at screening. With regard to safety, there was no AE with frovatriptan treatment nor any treatment-related effects on vital signs, ECGs, or clinical laboratory. The treatment was safe and well tolerated. To show efficacy of frovatriptan in the prophylactic treatment of episodic cluster headache further studies are required.

Date of the Report: 28.07.2008