the MENARINI group

This Synopsis 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

Name of company: Menarini International Operations Luxembourg	Summary table referring to Part of the dossier,	(For National Authority use only)
Name of finished product: Allegro®, Eumitan®, Migard®	Volume: Page:	
Name of active ingredient: frovatriptan		

Title:	A double-blind, cross-over patient preference study of frovatriptan versus rizatriptan for the acute treatment of migraine
Investigators:	A list of Investigators is provided in Appendix 16.1.4
Study Centers:	15 centers, thereof 7 centers in Germany, 3 centers in Greece, 3 centers in United Kingdom, 1 center in Finland and 1 center in Austria, a list of study centers is provided in Appendix 16.1.4
Dates of Study:	Date of first screening: 07 Sep 2007 Date of last visit: 28 Oct 2008
Clinical Phase:	IV
Publications:	No publication on this study available so far

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Objectives:	The primary objective of this study was to evaluate the subjective strength of preference for either study medication after having tested both of them on a number of between 1 and 3 attacks of migraine in a maximum period of 3 months. The secondary objectives of this study were: • Responses to the patient's preference questionnaire (PPQ) • Proportion of migraine episodes pain-free at 2 hours, at 4 hours, and sustained pain-free as derived from the headache intensity scale • Proportion of use of more than one dose of medication to treat an episode • Proportion of use of rescue medication to treat an episode • Proportion of recurrences • Time to recurrence • Change in headache intensity evaluated as mean over four time points of the difference between the intensity of headache measured immediately before taking the study drug and the intensity reported at each time point • Proportion of patients requiring early cross-over or early study discontinuation due to extreme study dissatisfaction with the assigned trial medication • Patient's satisfaction with the treatment as recorded after 48 hours. Clinical safety (adverse events [AEs], vital signs) was also monitored pre-study and at the end of each treatment period.
Methodology:	Phase IV, randomized, double-blind, cross-over, active-drug controlled study.

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Number of Patients Planned and Analyzed:	Planned size:	120 patients to be randomized (60 for each treatment group) in order to have at least 96 completed (48 patients for each treatment group)
	Randomized:	126 patients (62 frovatriptan as first treatment vs. 64 rizatriptan as first treatment)
	Safety Set:	124 patients (62 vs. 62 patients)
	Full Analysis Set (FAS):	106 patients (55 vs. 51 patients)
	Per-Protocol (PP) Set:	40 patients (21 vs. 19 patients)
Diagnosis and Main Selection Criteria:	Summary of Key Inclusion Criteria: • consenting ambulant male or non-pregnant female patients ≥ 18 and ≤ 65 years of age with history of migraine with or without aura according to the Intensity of Headache (IHS) criteria, with at least one but not more than six episodes per month during the last 6 months. Summary of Key Exclusion Criteria • history suggestive of ischemic heart disease (IHD; e.g. myocardial infarction, angina pectoris, coronary vasospasm, vasospastic [Prinzmetal's variant] angina) or any atherosclerotic disease (e.g. peripheral vascular disease) indicating an increased risk of coronary ischemia; *for patients with risk factors for CHD (especially for smokers, patients with diabetes mellitus, males > 40 years of age, postmenopausal females, patients with bundle branch heart block and patients with CHD in their family anamnesis) the Investigator had to consider carefully study participation with special attention to ECG results and anamnesis data [as per local Amendment in Germany dated 21 May 2007]* • symptomatic Wolff-Parkinson-White syndrome or cardiac arrhythmias associated with other cardiac accessory conduction pathway disorders • history of stroke or transient ischemic attack (TIA) • uncontrolled hypertension; *moderate severe or severe hypertension and uncontrolled slight hypertension (systolic blood pressure > 160 mmHg/diastolic blood pressure > 100 mmHg) [as per local*	

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Amendment in Germany dated 21 May 2007]

- history of basilar, hemiplegic or ophthalmoplegic migraine
- severe liver impairment (i.e., Child-Pugh score ≥ 7) *[as per local Amendment in Germany dated 21 May 2007, the criterion was in Germany: known or newly diagnosed liver diseases]*
- severe renal impairment (i.e., Creatinine Clearance [CrCl] <26 mL/min), renal disease, or renal failure *[as per local Amendment in Germany dated 21 May 2007, the criterion was in Germany: known or newly diagnosed renal diseases]*
- known or suspected intolerance of, or hypersensitivity or contraindications to any component of the trial medications, including inert substances (e.g. intolerance to galactose, Lapp's lactase deficiency, malabsorption of glucose-galactose, phenylketonuria)
- use of either test medication to treat any one of the last three episodes of migraine
- history of intolerance or inefficacy of at least two triptans for the treatment of migraine attacks
- current use of propanolol or ergotamine or its derivatives
- current use or use within the last 2 weeks of monoaminooxidase (MAO)-inhibitors
- abuse of alcohol, analgesics or psychotropic drugs *[as per local Amendment in Germany dated 21 May 2007, the criterion was in Germany: known or suspected abuse of alcohol, analgesics or psychotropic drugs]*
- severe concurrent medical condition that may affect the interpretation of clinical trial results
- pregnancy or breastfeeding
- participation in a clinical trial, currently or within the previous month
- inability or refusal to issue the informed consent
- more than six days of tension-type headache

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	• *signs of CHD in baseline ECG [as per local Amendment in Germany dated 21 May 2007].*
Dosage and Administration:	
Test Product	Frovatriptan 2.5 mg by oral route, one up to two doses per episode per day
Reference Therapy	Rizatriptan 10 mg by oral route, one up to two doses per episode per day
Duration of Treatment:	Each patient received the two study treatments in sequence, the sequence being determined by randomization. After having treated 3 episodes of migraine in not more than 3 months with the first treatment, the patient switched to the other treatment. After having treated 3 episodes of migraine in not more than 3 months with the second treatment, the patient indicated the preference for the first or second treatment. The patients' participation time in the study was therefore planned to be no longer than 6 months. As a consequence, the study duration per center was planned to be approximately 12 months. The estimated overall study duration was planned to be approximately 12 months

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Criteria for Evaluation:	**Primary Efficacy Variable** The primary efficacy variable was defined as the subjective strength of preference expressed by the patient on a 10 cm visual analogue scale (VAS) for the first or second treatment received. **Secondary Efficacy Variables** • Responses to the patient's preference questionnaire (PPQ) • Proportion of migraine episodes pain-free at 2 hours, at 4 hours, and sustained pain-free as derived from the headache intensity scale • Proportion of use of more than one dose of medication to treat an episode • Proportion of use of rescue medication to treat an episode • Proportion of recurrences • Time to recurrence • Change in headache intensity evaluated as mean over four time points of the difference between the intensity of headache measured immediately before taking the study drug and the intensity reported at each time point • Proportion of patients requiring early cross-over or early study discontinuation due to extreme study dissatisfaction with the assigned trial medication • Patient's satisfaction with the treatment as recorded after 48 hours. **Safety Variables** • Exposure to study medication • AEs and serious AEs (SAEs) • Vital signs (systolic and diastolic blood pressure, heart rate) • Changes in electrocardiogram (ECG).

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Statistical Methods:	The primary endpoint was the subjective strength of preference expressed for either treatment. This variable had to be available for the patient to be included into this analysis. No replacement was anticipated. This primary endpoint was analyzed on the Full Analysis Set (FAS) and for consistency reasons additionally on the PP Set. The primary analysis was performed using a closed test procedure overall and, depending on the overall result, within each sequence whether the recorded preference value differed significantly from 0. For this purpose, an Analysis of Variance (ANOVA) model was used that contained an intercept and sequence and center as explanatory factors. A secondary analysis included the comparison of the preference value between both sequences. In an additional secondary analysis of the primary endpoint, the proportion of preferences was analyzed as a dichotomous variable with the outcome "frovatriptan preferred" or "rizatriptan preferred". Preference values falling into the range of 0 to +1.0 in both directions were interpreted as "no preference" and excluded from the analysis. This dichotomous variable was evaluated by means of logistic regression with predictors including the factors treatment sequence, center, and Migraine Disability Assessment Scale (MIDAS) grade at baseline. The odds-ratio of the relevant impact of each of these predictors on the preference was estimated. This analysis was interpreted in a descriptive way only. The confirmatory analysis of the primary efficacy parameter was supported by a table displaying summary statistics for the reported preference value for each treatment sequence as well as a table displaying the dichotomous result of preference and a categorization of documented preference. The analysis of the secondary variables which was done for the FAS is presented in detail in Section 9.7.1.3.2. All safety and tolerability summaries were performed on the Safety Analysis Set. The proportion of patients with AEs was compared between treatments using Prescott's test. Vital signs data and the results of cardiovascular evaluation and ECG were summarized by descriptive statistics. Data were analyzed for possible changes over time by means of repeated measurement ANOVA, using gender, age and treatment sequence as adjusting factors. Subgroup analyses were performed for all efficacy parameters by age and gender and by triptan pre-treatment.

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Summary and Conclusions:

1. Efficacy Results:

1.1 Primary Efficacy Variable

The primary efficacy variable was defined as the subjective strength of preference expressed by the patient on a 10 cm VAS for the first or second treatment received. The scale ranged 0 to +5 in both directions.

1.1.1 Full Analysis Set (106 patients)

The patient preference value was (arithmetic mean ± standard deviation [median]) 3.66 ± 0.98 [4.00] in patients preferring frovatriptan and 3.40 ± 1.08 [3.00] in patients preferring rizatriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or rizatriptan ($p = 0.351$ in ANOVA test).

1.1.2 PP Set (40 patients)

The low number of patients included in the PP Set was caused by two main reasons, non adherence to treatment regimen and lack of attack documentation. Both main reasons were linked to the pathology and to the fact that this trial was conducted closely to realistic treatment conditions in a number of countries. However, PP results reflected the results of the Full Analysis, i.e. the violations did not affect the results and the study was well conducted.

The overall patient preference value was (arithmetic mean ± standard deviation [median]) 3.70 ± 0.83 [4.00] in patients preferring frovatriptan and 3.66 ± 1.04 [4.00] in patients preferring rizatriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or rizatriptan ($p = 0.358$ in ANOVA test).

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1.2 Secondary efficacy variables

1.2.1 Full Analysis Set (106 patients)

Patients with relevant preference

In total, of the 84 (79.2%) patients with a relevant preference, i.e. a preference value of greater than +1.0 in any direction, 36 (34.0%) patients expressed a preference for frovatriptan while 48 (45.3%) patients expressed a preference for rizatriptan. In the Full Analysis Set, 22 patients expressed no preference.

Responses to the patient's preference questionnaire (PPQ)

Rapid activity was the most influential reason for both treatments, but the study results show that there are multiple important reasons to prefer a migraine medication. These influential reasons represented completely different characteristics, e.g. rapid activity, reduction of severity and protracted activity, indicating an important difference between the drug profiles.

Total number of patients with expressed preference	**Frovatriptan (n=36)**	**Rizatriptan (n=48)**
Patient preference most influential property	**n (%)**	**n (%)**
Rapid activity	5 (13.9)	16 (33.3)
Reduction of severity	6 (16.7)	6 (12.5)
Complete analgesia	2 (5.6)	8 (16.7)
Protracted activity	7 (19.4)	1 (2.1)
No side effects	3 (8.3)	4 (8.3)
Prevention of aggravation	2 (5.6)	2 (4.2)

Proportion of migraine episodes pain-free at 2 hours and at 4 hours

The proportion of pain-free episodes under frovatriptan was 17.7% at 2 hours and 43.6% at 4 hours and under rizatriptan 31.4% at 2 hours and 60.3% at 4 hours, i.e., the proportion of pain-free episodes was significantly higher under treatment with rizatriptan than under treatment with frovatriptan both after 2 and 4 hours ($p < 0.001$ in all logistic regression and GEE tests). This was also applicable if the patients were subdivided by their expressed preference.

Change in headache intensity

Overall, the mean improvement of headache on a scale from 3 to 0 was similar in both treatments with an arithmetic mean ± standard deviation [median] of 1.29 ± 0.80 [1.25] points under treatment with frovatriptan and with 1.30 ± 0.83 [1.25] points under treatment with rizatriptan. The headache intensity was significantly more improved under rizatriptan at 2 and 4 hours ($p<0.001$ in GEE-test), while it was significantly more improved under frovatriptan at 24 hours ($p<0.001$ in GEE-test) and 48 hours ($p=0.010$ in GEE-test), indicating an important difference between the drug profiles.

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Proportion of recurrences and time to recurrence
The proportion of patients with at least one recurring episode as well as the proportion of recurring episodes was significantly lower under frovatriptan with 33 (39.3%) patients and 42 (17.1%) episodes than under treatment with rizatriptan with 54 (59.3%) patients and 88 (35.6%) episodes ($p = 0.005$ for patients and $p < 0.001$ for episodes in logistic regression and $p = 0.003$ for patients and $p < 0.001$ for episodes in GEE tests). Of 42 recurrent episodes under treatment with frovatriptan, 3 episodes had a time to recurrence of up to 4 hours, 27 episodes had a time to recurrence of more than 4 hours up to 24 hours and 12 episodes had a time to recurrence of more than 24 up to 48 hours. Of 88 recurrent episodes under treatment with rizatriptan, 2 episodes had a time to recurrence of up to 4 hours, 67 episodes had a time to recurrence of more than 4 hours up to 24 hours and 19 episodes had a time to recurrence of more than 24 up to 48 hours. The median time to recurrence was 17.3 hours under treatment with frovatriptan, and 16.5 hours under treatment with rizatriptan.

Proportion of use of more than one dose of medication to treat an episode and of rescue medication to treat an episode
Each migraine episode was intended to be treated with one or up to two doses only, with a limit of two doses in 24 hours. However, since a migraine attack could last up to 72 hours, each patient was provided with 6 unit doses for each of the three anticipated attacks. There were less patients and episodes with at least two medication doses within an episode under treatment with frovatriptan with 92 (87.6%) patients and 206 (67.3%) episodes compared to treatment with rizatriptan with 95 (90.5%) patients and 225 (74.0%) episodes ($p = 0.046$ in GEE-test). The proportions of patients and episodes with use of rescue medication within an episode were similar under treatment with frovatriptan with 46 (43.8%) patients and 79 (25.7%) episodes compared to treatment with rizatriptan with 39 (37.1%) patients and 64 (21.1%) episodes without statistically significant differences between treatments.

Sustained pain-free episodes
Sustained pain-free episodes were observed in 34 (11.3%) episodes under treatment with frovatriptan and in 47 (15.7%) episodes under treatment with rizatriptan without statistically significant differences between treatments. As an AE was reported only for two of the sustained pain-free episodes, all analyses of sustained-free episodes with certain AEs revealed nearly identical results.

Proportion of patients requiring early cross-over or early study discontinuation
Only 2 (1.9%) patients under treatment with frovatriptan and 3 (2.8%) patients under treatment with rizatriptan required an early cross-over or study discontinuation.

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Secondary efficacy variables (continued)

Patient satisfaction with the treatment as recorded after 48 hours
Patients were well satisfied with both medications. In the Full Analysis Set, the mean satisfaction (arithmetic mean ± standard deviation [median]) was 2.48 ± 1.01 [2.33] points under treatment with frovatriptan and 2.60 ± 1.03 [2.67] points under treatment with rizatriptan.

1.2.2 PP Set (40 patients)

Patients with relevant preference
Of the 35 (87.5%) patients with a relevant preference, i.e. a preference value of greater than +1.0 in any direction, 14 (35.0%) patients expressed preference for frovatriptan, while 21 (52.5%) patients expressed preference for rizatriptan.

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Secondary efficacy variables (continued)

Responses to the patient's preference questionnaire (PPQ)

Rapid activity was the most influential reason for both treatments, but the study results show that there are multiple important reasons to prefer a migraine medication. There is a clear difference in the most influential properties associated with each study medication, one opposite to the other (e.g. "complete analgesia" versus "protracted activity"). These influential reasons represented completely different characteristics, e.g. rapid activity, reduction of severity and protracted activity, indicating an important difference between the drug profiles.

.Total number of patients with expressed preference	Frovatriptan (n=14)	Rizatriptan (n=21)
Patient preference most influential property	**n (%)**	**n (%)**
Rapid activity	3 (21.4)	8 (38.1)
Complete analgesia	0 (0.0)	5 (23.8)
Protracted activity	5 (35.7)	0 (0.0)
Reduction of severity	2 (14.3)	2 (9.5)
Prevention of aggravation	0 (0.0)	1 (4.8)
No side effects	0 (0.0)	1 (4.8)
Single dose	1 (7.1)	0 (0.0)
No single most influential property (zero entered)	0 (0.0)	1 (4.8)

Proportion of migraine episodes pain-free at 2 hours, at 4 hours

The proportion of pain-free episodes was significantly higher under treatment with rizatriptan than under treatment with frovatriptan both after 2 and 4 hours ($p = 0.002$ and $p = 0.004$ for 2 hours and $p = 0.056$ and $p = 0.011$ for 4 hours in logistic regression and GEE tests, respectively). This was also applicable if the patients were subdivided by their expressed preference.

Change in headache intensity

Overall, the mean improvement of headache on a scale from 3 to 0 was 1.44 ± 0.74 [1.50] points under treatment with frovatriptan and with 1.53 ± 0.73 [1.50] points under treatment with rizatriptan. The mean overall headache intensity at 48 hours was 1.8 ± 0.9 [2.0] points under treatment with frovatriptan and 1.7 ± 1.0 [2.0] points under treatment with rizatriptan. The headache intensity was significantly more improved under rizatriptan at 2 hours ($p<0.001$ in GEE-test) and 4 hours ($p=0.037$ in GEE-test), while it improved more under frovatriptan at 24 hours with a statistically significant difference ($p=0.030$ in GEE-test) and a favorable trend at 48 hours.

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Secondary efficacy variables (continued)

Proportion of recurrences and time to recurrence
PP results were similar to those of the Full Analysis Set.

Proportion of use of more than one dose of medication to treat an episode and of rescue medication to treat an episode
PP results were similar to those of the Full Analysis Set.

Sustained pain-free episodes
Under both treatments, a similar proportion of episodes was sustained pain-free without statistically significant differences between treatments.

Patient's satisfaction with the treatment as recorded after 48 hours
Patients were well satisfied with both medications. Overall, PP results were similar to those of the Full Analysis Set.

2. Safety Results:

Overall, 111 AEs were reported in 50 (40.3%) patients, thereof 42 AEs in 26 (22.8%) patients during treatment with frovatriptan, 56 AEs in 36 (30.0%) patients under treatment with rizatriptan and 6 pre-treatment AEs in 5 (4.0%) patients without statistically significant differences, but a favorable trend for frovatriptan. Seven of the 111 AEs could not be unambiguously assigned to one of the treatments. In 19 (15.3%) patients, 42 AEs with relationship of certain, probable, possible or unlikely were reported, thereof 17 events in 10 (8.8%) patients under treatment with frovatriptan and 25 AEs in 16 (13.3%) patients under treatment with rizatriptan. Only 2 events were reported with severe intensity, a case of vomiting in patient 205138 and a case of tension type headache in patient 207122. Only in 2 (1.7%) patients under treatment with rizatriptan AEs led to withdrawal. Chest discomfort was reported in 2 (1.7%) patients under treatment with rizatriptan and none under treatment with frovatriptan. Three SAEs were reported, thereof thyroid disorder and hysterectomy under treatment with frovatriptan and a meniscus lesion under treatment with rizatriptan. No deaths, drug-related SAEs or SAEs leading to withdrawal were reported. There were no relevant findings with regard to vital signs or other safety-related observations. Both treatments were safe and well tolerated.

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Conclusions:

Both frovatriptan and rizatriptan were effective in treatment of migraine. Patients were well satisfied with both medications. Safety results were slightly in favor of frovatriptan. Both treatments were safe and well tolerated.
This was the first study in line with the IHS guideline that states that patient preference should be used as primary parameter. The concept of patient preference was shown to be valid as 84 of 106 (79.2%) patients expressed a relevant preference and no single reason for patient preference exists. There is no single most important drug attribute, but there are multiple important factors that influence the patient preference. Both drugs confirmed their profile, frovatriptan as long-acting, rizatriptan as short-acting medication. The proportion of patients with at least one recurring episode as well as the proportion of recurring episodes was significantly lower under frovatriptan than under treatment with rizatriptan and there were also less patients and episodes with at least two medication doses within an episode under treatment with frovatriptan compared to treatment with rizatriptan up to 48 hours.

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