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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.

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## 2. Synopsis

| Name of company:<br>Laboratori Guidotti S.p.A. | Summary table referring to Part of the dossier, | (For National Authority use only) |
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| Name of finished product:<br>Rilamig® | Volume:<br>Page: | |
| Name of active ingredient:<br>Frovatriptan | | |

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| Title: | Evaluation of the efficacy of frovatriptan versus almotriptan for the acute treatment of migraine |
| Investigators: | A list of Investigators is provided in Appendix 16.1.4 |
| Study Centers: | 12 Italian centers. A list of study centers is provided in Appendix 16.1.4 |
| Dates of Study: | Date of first screening: 30/10/2007<br>Date of last visit: 30/01/2009 |
| Clinical Phase: | IV |
| Publications: | Main results of this study have been published in Bartolini M et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. J Headache Pain 2011. |
| 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.<br>The secondary objectives of this study were:<br>• Responses to the patient's preference questionnaire (PPQ)<br>• Proportion of migraine episodes pain-free at 2 hours, at 4 hours, and sustained pain-free as derived from the headache intensity scale<br>• Proportion of use of more than one dose of medication to treat an episode<br>• Proportion of use of rescue medication to treat an episode<br>• Proportion of recurrences<br>• Time to recurrence<br>• 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 (particularly at 2 and 4 hours)<br>• Proportion of patients requiring early cross-over or early study discontinuation due to extreme study dissatisfaction with the assigned trial medication<br>• Patient's satisfaction with the treatment as recorded after 48 hours.<br>Clinical safety (adverse events or AEs, vital signs) was also monitored during each treatment period. |
| Methodology: | Phase IV, randomized, double-blind, cross-over, active-drug controlled |

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| | study. | |
| 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)<br>Randomized: 133 patients (65 frovatriptan as first treatment vs.68 almotriptan as first treatment)<br>Safety Set: 123 patients (61 vs. 62 patients)<br>Full Analysis Set (FAS): 114 patients (59 vs. 55 patients)<br>Per-Protocol (PP) Set: 65 patients (33 vs.32 patients) | |
| Diagnosis and Main Selection Criteria: | Summary of Key Inclusion Criteria:<br>• 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 International Headache Society (IHS) criteria, with at least one but not more than six episodes per month during the last 6 months<br>Summary of Key Exclusion Criteria<br>• 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;<br>• Symptomatic Wolff-Parkinson-White syndrome or cardiac arrhythmias associated with other cardiac accessory conduction pathway disorders<br>• History of stroke or transient ischemic attack (TIA)<br>• Uncontrolled hypertension;<br>• History of basilar, hemiplegic or ophthalmoplegic migraine<br>• Severe liver impairment (i.e., Child-Pugh score C)<br>• Severe renal impairment (i.e., Creatinine Clearance [CrCl] <26 mL/min), renal disease, or renal failure<br>• 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)<br>• Use of either test medication to treat any one of the last three episodes of migraine<br>• History of intolerance or inefficacy of at least two triptans for the treatment of migraine attacks | |

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| | • Current use of propranolol or ergotamine or its derivatives<br>• Current use or use within the last 2 weeks of monoaminooxidase (MAO)-inhibitors<br>• Abuse of alcohol, analgesics or psychotropic drugs<br>• Severe concurrent medical condition that may affect the interpretation of clinical trial results<br>• Pregnancy or breastfeeding<br>• Participation in a clinical trial, currently or within the previous month<br>• Inability or refusal to issue the informed consent<br>• More than six days of tension-type headache | |
| Dosage and Administration: | | |
| Test Product | Frovatriptan 2.5 mg by oral route, one up to two doses per episode per day | |
| Reference Therapy | Almotriptan 12.5 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 no more than 3 months with the first treatment, the patient switched to the other treatment. After having treated 3 episodes of migraine in no 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. | |
| Criteria for Evaluation: | Primary Efficacy Variable<br>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.<br>Secondary Efficacy Variables<br>• Responses to the patient's preference questionnaire (PPQ)<br>• Proportion of migraine episodes pain-free at 2 hours, at 4 hours, and sustained pain-free as derived from the headache intensity scale<br>• Proportion of use of more than one dose of medication to treat an episode<br>• Proportion of use of rescue medication to treat an episode<br>• Proportion of recurrences | |

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| | • Time to recurrence<br>• 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<br>• Proportion of patients requiring early cross-over or early study discontinuation due to extreme study dissatisfaction with the assigned trial medication<br>• Patient's satisfaction with the treatment as recorded after 48 hours.<br><br>Additional secondary analysis were the evaluation of pain relief episodes at 2 and 4 hours.<br><br>Safety Variables<br><br>• Exposure to study medication<br>• AEs and serious AEs (SAEs)<br>• Vital signs (systolic and diastolic blood pressure, heart rate)<br>• Changes in electrocardiogram (ECG) |
| Statistical Methods: | The primary endpoint was the subjective strength of preference expressed for either treatment. This variable had to be available in order to include the patient in the analysis. No replacement was anticipated.<br><br>This primary endpoint was analyzed on the 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.<br><br>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 "almotriptan 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. |

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| | 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.<br>The analysis of the secondary variables which was done for the FAS is presented in detail in Section 9.7.1.3.2. Some of the secondary analyses were also applied to the PP set, when deemed useful.<br>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. |

**Summary and Conclusions:**

**Efficacy Results:**

**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 from 0 to +5, in both directions.

**FAS (114 patients)**

The patient preference value was 3.05±1.33 in patients preferring frovatriptan and 3.44±1.33 in patients preferring almotriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or almotriptan.

**PP Set (65 patients)**

The number of patients included in the PP Set was much lower than that included in the FAS analysis. This was mainly due to the exclusion of subjects taking more than two study drug doses over the 24 hours followed by use of rescue medication instead of the second dose of study drug, treatment of less than 3 attacks per period, and use of forbidden medication. All reasons were linked to the pathology and to the fact that this trial was conducted closely to realistic treatment conditions. However, PP results reflected the results of the FAS, i.e. the violations did not affect the results and the study was well conducted.
In the PP set the overall patient preference value was 3.21±1.44 in patients preferring frovatriptan and 3.16±1.34 in patients preferring almotriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or almotriptan.

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**Secondary Efficacy Variables**

Patients with relevant preference

In the FAS set, of the 73 (68.2%) patients with a relevant preference, i.e. a preference value greater than +1.0 in any direction, 33 (28.9%) patients expressed preference for frovatriptan, while 39 (34.2%) patients expressed preference for almotriptan, with no statistically significant between group differences.

Responses to the patient's preference questionnaire (PPQ)

The most common reason for preferring one triptan to the other was the rapid action (53.2% of subjects), followed by reduction in migraine severity (14.3%) and prevention of aggravation (7.8%). Interestingly patients chose more than one preference, this meaning that preference was based on multiple factors.

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

The proportion of pain-free episodes at 2 hours was not significantly different between frovatriptan (99/327, 30.3%) and almotriptan (104/329, 31.6%). This was the case also for pain free episodes at 4 hours (frovatriptan 55.6% and almotriptan 58.7%).

Headache intensity

Overall mean headache intensity was simlarly reduced by both treatments at 2 hours (frovatriptan 1.26±1.04 vs. almotriptan 1.20±1.03), 4 hours (0.74±0.98 vs. 0.75±1.01), 24 hours (0.41±0.79 vs. 0.46±0.84) and 48 hours (0.31±0.76 vs. 0.37±0.79).

Proportion of recurrences and time to recurrence

The frequency of recurring episodes was significantly ($p<0.05$) lower under frovatriptan (30/327, 9.2%) than under almotriptan (46/329, 14.0%).
Time to recurrence evaluated by Kaplan-Meier curves, indicated a significant ($p<0.05$) between-treatments difference in the hazard of recurrence over the 48 hour observation period.

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.. Under frovatriptan there were 173 (52.7%) episodes treated with two or more doses of study medication, 184 (55.8%) under almotriptan. No statistically significant between treatment difference were ever observed.
The proportions of episodes with use of rescue medication within an episode were also similar under both treatments (59/328, 18.0% with frovatriptan and 66/330, 20.0% with almotriptan), without statistically significant differences between treatments.

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Sustained pain-free episodes

Sustained pain-free episodes were observed in 69 (21.1%) episodes treated with frovatriptan and in 58 (17.6%) episodes treated with almotriptan, without statistically significant differences between treatments.

Proportion of patients requiring early cross-over or early study discontinuation

No patients required early cross-over or early study discontinuation.

Patient satisfaction with the treatment as recorded after 48 hours

Patients were well satisfied with both medications. The proportion of episodes for which the overall patient's grade of satisfaction was good or very good was not significantly different between frovatriptan and almotriptan (good: 34.0% vs. 30.9%; very good: 9.0% vs. 11.1%).

Proportion of migraine episodes with pain-relief at 2 hours and at 4 hours

The proportion of pain-relief episodes at 2 and 4 hours was 53.8% and 74.9% under frovatriptan and 55.8% and 72.0% under almotriptan. The between treatment difference was never statistically significant.

**PP Set (65 patients)**

Patients with relevant preference

Of the patients with a relevant preference, i.e. a preference value greater than +1.0 in any direction, 16 (24.6%) patients expressed preference for frovatriptan, while 22 (33.9%) patients expressed preference for almotriptan. No statistically significant difference was observed between the two treatments.

Responses to the patient's preference questionnaire (PPQ)

This analysis was not performed in the PP set.

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

The proportion of pain-free episodes at 2 and 4 hours was not significantly different between frovatriptan (29.7% and 56.9%) and almotriptan (34.4% and 61.0%).

Headache intensity

This analysis was not performed in the PP set.

Proportion of recurrences and time to recurrence

The proportion of recurring episodes was significantly ($p<0.05$) lower under frovatriptan than under almotriptan, also in the PP set (frovatriptan 19.0% vs. 35.8% under almotriptan).

Proportion of use of more than one dose of medication to treat an episode and of rescue

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medication to treat an episode

This analysis was not performed in the PP set.

Sustained pain-free episodes

PP results were similar to those of the FAS with a similar proportion of sustained pain free episodes under frovatriptan (23.1%) and almotriptan (22.6%).

Proportion of patients requiring early cross-over or early study discontinuation

No patients required early cross-over or early study discontinuation.

Patient's satisfaction with the treatment as recorded after 48 hours

This analysis was not performed in the PP set.

Proportion of migraine episodes with pain-relief at 2 hours and at 4 hours

The proportion of pain-relief episodes at 2 and 4 hours was not significantly different between the two treatments, as for the FAS (frovatriptan: 52.2% and 76.4%; almotriptan: 61.5% and 79.1%).

**Safety Results:**

Overall, 52 AEs were reported in 19 (15.4%) patients, thereof 17 AEs in 8 (13.1%) patients during frovatriptan-almotriptan sequence and 35 AEs in 11 (17.7%) patients during almotriptan-frovatriptan sequence. The number of AEs under frovatriptan were 28 and 24 under almotriptan. Most of the AEs were of a mild or moderate intensity, and no deaths were reported during the study. Two SAEs, not related to study drug, were reported in 1 patient treated with frovatriptan. No patients under almotriptan prematurely withdrew from the study, while 1 patient under frovatriptan was dropped-out for occurrence of two drug-related AEs.

In 9 (7.3%) patients, 31 treatment related AEs were reported, thereof 3 events in 2 (3.3%) patients under frovatriptan-almotriptan sequence and 28 AEs in 7 (11.3%) patients under almotriptan-frovatriptan sequence. The number of drug-related AEs was 13 under frovatriptan and 18 under almotriptan. There was a slightly larger prevalence of cardiovascular symptoms during almotriptan treatment.

There were no relevant findings with regard to vital signs or other safety-related observations. Both treatments were safe and well tolerated.

**Conclusions:**

Both frovatriptan and almotriptan were effective in treatment of migraine. Patients were well satisfied with both medications. Safety results showed a similar tolerability of the two drugs.
This was the first direct comparative study between frovatriptan and almotriptan using patient preference as primary parameter, following IHS guideline indications. The concept of patient

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| preference was shown to be valid as 72 of 114 (63.2%) patients expressed a relevant prefererence 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. Interestingly, frovatriptan was chosen for its rapid activity by 51.4% of patients.This prefererence was confirmed by clinical data regarding the immediate effect of frovatriptan. Both drugs confirmed their profile, with a similar efficacy in the immediate (pain free and pain relief at 2 and 4 hours), a similar tolerability, but frovatriptan showed lower risk of recurrence over the whole 48 hour observation period after intake.<br><br>Date of the final report: 31 March 2011 | | |