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

Name of company: Istituto Lusofarmaco d'Italia S.p.A.	Summary table referring to Part of the dossier,	(For National Authority use only)
Name of finished product: Auradol®	Volume: Page:	

Name of active ingredient: Frovatriptan	
Title:	A 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 Italian centers. A list of study centers is provided in Appendix 16.1.4
Dates of Study:	Date of first screening: 03/09/2007 Date of last visit: 15/09/2008
Clinical Phase:	IV
Publications:	Main results of this study have been published in Savi L et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. J Headache Pain 2010
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 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 (particularly at 2 and 4 hours) • 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 or AEs, vital signs) was also monitored during each treatment period.

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Methodology:	Phase IV, randomized, double-blind, cross-over, active-drug controlled study.	
Number of Patients Planned and Analyzed:	Planned size: Randomized: Safety Set: Full Analysis Set (FAS): Per-Protocol (PP) Set:	120 patients to be randomized (60 for each treatment group) in order to have at least 96 completed (48 patients for each treatment group) 148 patients (75 frovatriptan as first treatment vs.73 rizatriptan as first treatment) 137 patients (73 vs. 64 patients) 125 patients (65 vs. 60 patients) 96 patients (52 vs. 44 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 International Headache Society (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; • 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; • History of basilar, hemiplegic or ophthalmoplegic migraine • Severe liver impairment (i.e., Child-Pugh score C) • Severe renal impairment (i.e., Creatinine Clearance [CrCl] <26 mL/min), renal disease, or renal failure • 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	

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	• History of intolerance or inefficacy of at least two triptans for the treatment of migraine attacks • Current use of propranolol 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 • 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
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 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 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

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	• 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. Additional secondary analysis were the evaluation of pain relief episodes at 2 and 4 hours, evaluation of some efficacy parameters in the subgroup of women with menstrual migraine, patients characteristic according to preference and evaluation of efficacy at 2 hours by patient preference. Safety Variables • Exposure to study medication • AEs and serious AEs (SAEs) • Vital signs (systolic and diastolic blood pressure, heart rate) • 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. 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

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	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. Some of the secondary analyses were also applied to the PP set, when deemed useful. 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. A t-test of Student was used to compared changes in migraine intensity from baseline between the two treatments at 2, 4, 24 and 48 hours.

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 (125 patients)

48 patients (38.4%) treated with frovatriptan and 56 patients (44.8%) treated with rizatriptan expressed a preference for one treatment or the other. The patient preference value was 2.90±1.28 (median: 3.00) in patients preferring frovatriptan and 3.18±1.07 (3.00) in patients preferring rizatriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or rizatriptan.

PP Set (96 patients)

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The number of patients included in the PP Set was lower than that included in the FAS analysis. This was mainly due to the exclusion of subjects treating <3 attacks per period and to the use of rescue medication instead of the second dose of study drug. Both 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 42 patients (43.7%) treated with frovatriptan and 40 patients (41.7%) treated with rizatriptan expressed a preference for one treatment or the other. The overall patient preference value was 2.88±1.32 (median: 3.00) in patients preferring frovatriptan and 3.18±1.13 (3.00) in patients preferring rizatriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or rizatriptan.

Secondary Efficacy Variables

Patients with relevant preference

Of the 92 (73.6%) patients with a relevant preference, i.e. a preference value greater than +1.0 in any direction, 39 (42.4%) patients expressed preference for frovatriptan, while 53 (57.6%) patients expressed preference for rizatriptan, 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, followed by reduction in migraine severity, no side effects, recovery of functioning and complete analgesia. These preferences were assigned by at least one third of the sample. 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 (n=117, 32.8%) and rizatriptan (n=141, 39.0%). At 4 hours pain free episodes were significantly (p=0.023 logistic regression and p=0.038 GEE test) less frequent in the frovatriptan group (n=202, 56.6%) than in the rizatriptan group (n=238, 65.7%).

Change in headache intensity

The change in the average score of migraine intensity from baseline (i.e. the improvement in headache intensity) was similar between the two drugs at 2 hours (0.75±1.10 frovatriptan vs. 0.88±1.00 rizatriptan, p=0.096) and 4 hours (1.24±1.06 frovatriptan vs. 1.39±0.95 rizatriptan, p=0.052), while it was significantly larger with frovatriptan at 24 hours (1.64±0.97 vs. 1.42±1.02 rizatriptan, p=0.003) and at 48 hours (1.80±0.86 vs. 1.61±1.01 rizatriptan, p=0.007).

Proportion of recurrences and time to recurrence

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The proportion of patients with at least one recurring episode tended to be lower under frovatriptan (n=33; 50.8%) than under rizatriptan (n=40; 66.7%) but the difference was not statistically significant, when explored both with GEE test and logistic regression. Conversely, the frequency of recurring episodes was significantly lower under frovatriptan (21.6%) than under rizatriptan (32.2%; $p<0.0001$ GEE test and $p=0.001$ logistic regression).
Time to recurrence evaluated by Kaplan-Meier curves, indicated a significantly ($p<0.05$) lower hazard of recurrence under frovatriptan.

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. The patients and episodes treated with two doses of study medication were similarly distributed between the two treatments groups. Under frovatriptan there were 60 (92.3%) patients and 110 (30.8%) episodes treated with a second dose of study medication. The corresponding figure under rizatriptan was 55 (91.7%) and 122 (33.7%). Overall 67 (18.8%) episodes under frovatriptan and 74 (20.4%) under rizatriptan were treated with more than two doses of study medication. No statistically significant between treatment difference were ever observed.
The proportions of patients and episodes with use of rescue medication within an episode were also similar under treatment with frovatriptan, with 36 (55.4%) patients and 71 (19.9%) episodes, compared to treatment with rizatriptan, with 31 (51.7%) patients and 59 (16.3%) episodes, without statistically significant differences between treatments.

Sustained pain-free episodes

Sustained pain-free episodes were observed in 92 (25.8%) episodes treated with frovatriptan and in 80 (22.1%) episodes treated with rizatriptan, without statistically significant differences between treatments.

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

Only 1 (1.5%) patients under treatment with frovatriptan and 1 (1.7%) patients under treatment with rizatriptan required an early cross-over or 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 (42.4%) and rizatriptan (41.1%).

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

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The proportion of pain-relief episodes at 2 and 4 hours was 55.2% and 70.1% under frovatriptan and 61.7% and 79.2% under rizatriptan, The between treatment difference was significant at 4 hours (p=0.026 logistic regression and p=0.040 GEE test).

Menstrual migraine

There were no statistically significant differences in the proportion of pain free episodes at 2 and 4 hours, in the use of two medications and rescue medication. Risk of recurrence in women with menstrual migraine was significantly lower (p<0.01) under frovatriptan.

Other subgroup analyses

There were no clinically relevant differences in age and gender distribution in patients preferring one drug or the other. There were also no clinically relevant differences between the two treatments in drug efficacy according to preference.

PP Set (96 patients)

Patients with relevant preference

Of the 71 (74.0%) patients with a relevant preference, i.e. a preference value greater than +1.0 in any direction, 33 (46.5%) patients expressed preference for frovatriptan, while 38 (53.5%) patients expressed preference for rizatriptan. No statistically significant difference was observed between the two treatments.

Responses to the patient's preference questionnaire (PPQ)

As for the FAS the most influential reason for choosing one treatment or the other was the rapid action, followed by reduction in migraine severity, no side effects, recovery of functioning and complete analgesia (preference assigned by at least one-third of the patients).

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 (37.2% and 62.5%) and rizatriptan (40.3% and 67.0%).

Change in headache intensity

This analysis was not performed in the PP set.

Proportion of recurrences and time to recurrence

The proportion of patients having at least one recurrence was significantly lower under frovatriptan (48.1% vs. 65.9% rizatriptan; p=0.034 logistic regression). In the same population, the proportion of migraine episodes that recurred was 21.2% under frovatriptan and 31.6% under rizatriptan (p=0.001 logistic regression and p=0.001 GEE test). Also in this population cumulative hazard of recurrence at 48 hours was significantly (p<0.05) lower under frovatriptan

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than under rizatriptan.

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 FAS.

Sustained pain-free episodes

This analysis was not performed in the PP set.

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

This analysis was not performed in the PP set.

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.

Menstrual migraine

This analysis was not performed in the PP set.

Other subgroup analyses

Analysis of age and gender distribution according to preference in the PP set gave similar results to the FAS. Evaluation of efficacy at 2 hours by patient preference was not carried out in the PP set.

Safety Results:

Overall, 160 AEs were reported in 46 (33.6%) patients, thereof 44 AEs in 18 (24.7%) patients during treatment frovatriptan-rizatriptan sequence and 116 AEs in 28 (43.8%) patients during rizatriptan-frovatriptan sequence. Most of the AEs were of a mild or moderate intensity, and no deaths, SAEs or SAEs leading to withdrawal were reported during the study. No patients under frovatriptan prematurely withdrew from the study, while 2 patients under rizatriptan did (one patient for dizziness and one for left ankle edema).

In 21 (15.3%) patients, 89 treatment related AEs were reported, thereof 23 events in 8 (11.0%) patients under frovatriptan-rizatriptan sequence and 66 AEs in 13 (20.3%) patients under rizatriptan-frovatriptan sequence.

Considering treated attacks, 65 AEs under frovatriptan and 93 under rizatriptan were recorded. Two AEs could not be classified, because the start date was unknown. 39 AEs under frovatriptan

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and 50 under rizatriptan were treatment related. Attacks with at least one treatment related AE were 27 under frovatriptan and 25 under rizatriptan.
Cardiovascular symptoms (tachycardia, thoracic constriction or pain) were much more frequent in the rizatriptan treatment group (12 AEs vs. 1, $p<0.01$).

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 rizatriptan were effective in treatment of migraine. Patients were well satisfied with both medications. Safety results were slightly in favor of frovatriptan, but both treatments were safe and well tolerated.
This was the first direct comparative study between frovatriptan and rizatriptan using patient preference as primary parameter, following IHS guideline indications. The concept of patient preference was shown to be valid as 104 of 125 (83.2%) 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. Interestingly, frovatriptan was chosen by 70.8% of patient for its rapid activity. This preference was confirmed by clinical data: as a matter of fact, frovatriptan showed pain free and pain relief rates at 2 hours similar to those observed under rizatriptan. Besides, frovatriptan showed a more sustained effect than rizatriptan, the proportion of patients with at least one recurring episode as well as the proportion of recurring episodes being significantly lower under frovatriptan than under rizatriptan.

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