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:	Evaluation of the efficacy of frovatriptan versus zolmitriptan for the acute treatment of migraine
Investigators:	A list of Investigators is provided in Appendix 16.1.4
Study Centers:	16 Italian centers. A list of study centers is provided in Appendix 16.1.4
Dates of Study:	Date of first screening: 09/07/2007 Date of last visit: 18/12/2008
Clinical Phase:	IV
Publications:	Main results of this study have been published in Tullo V et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. Neurol Sci 2010;31(Suppl.1):S51-54.
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:~~ 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 (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.

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		

Methodology:	Phase IV, randomized, double-blind, cross-over, active-drug controlled 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)
	Randomized:	133 patients (68 frovatriptan as first treatment vs.65 zolmitriptan as first treatment)
	Safety Set:	121 patients (63 vs. 58 patients)
	Full Analysis Set (FAS):	107 patients (57 vs. 50 patients)
	Per-Protocol (PP) Set:	68 patients (41 vs.274 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	

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		
	• 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	Zolmitriptan 2.5 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 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	

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		

	• 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, and patients characteristic according to 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 "zolmitriptan preferred". Preference values falling into the range of 0 to +1.0 in both directions were interpreted as "no

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		

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.

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 (107 patients)

36 patients (33.6%) treated with frovatriptan and 46 patients (43.0%) treated with zolmitriptan expressed a preference for one treatment or the other. The patient preference value was 2.85±1.33 (median: 3.00) in patients preferring frovatriptan and 3.04±1.28 (3.00) in patients preferring zolmitriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or zolmitriptan.

PP Set (68 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 treating <3 attacks per period and to

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		

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 20 patients (29.4%) treated with frovatriptan and 33 patients (48.5%) treated with zolmitriptan expressed a preference for one treatment or the other. The overall patient preference value was 3.05±1.41 (median: 3.00) in patients preferring frovatriptan and 3.04±1.23 (3.00) in patients preferring zolmitriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or zolmitriptan.

Secondary Efficacy Variables

Patients with relevant preference

Of the 73 (68.2%) patients with a relevant preference, i.e. a preference value greater than +1.0 in any direction, 30 (41.1%) patients expressed preference for frovatriptan, while 43 (58.9%) patients expressed preference for zolmitriptan, 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, protracted activity 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=80, 26.3%) and zolmitriptan (n=94, 31.4%). This was the case also for pain free episodes at 4 hours (frovatriptan 56.6% and zolmitriptan 64.5%).

Change in headache intensity

Migraine intensity was always significantly ($p<0.0001$) reduced as compared to baseline. Overall the mean improvement of headache was similar under frovatriptan an zolmitriptan at 2 hours (0.85±0.90 vs. 0.91±0.85), 4 hours (1.36±1.02 vs. 1.46±0.91), 24 hours (1.74±0.88 vs. 1.75±0.91) and 48 hours (1.88±0.83 vs. 1.89±0.84).

Proportion of recurrences and time to recurrence

The proportion of patients with at least one recurring episode was similar for the frovatriptan-zolmitriptan (n=28; 49.1%) and zolmitriptan-frovatriptan sequence (n=29; 58.0%). This was the case also for the frequency of recurring episodes (frovatriptan 20.7% vs. zolmitriptan 23.7%).

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		

Time to recurrence evaluated by Kaplan-Meier curves, indicated a significant between-treatments difference in the hazard of recurrence between 4 and 16 hours.

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 107 (35.2%) episodes treated with a second dose of study medication, 115 (38.5% under zolmitriptan.. Overall 138 (45.4%) episodes under frovatriptan and 143 (47.8%) under zolmitriptan 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 both treatments. The proportion of episodes treated with the rescue medication was 15.1% under frovatriptan and 15.4% under zolmitriptan, without statistically significant differences between treatments.

Sustained pain-free episodes

Sustained pain-free episodes were observed in 61 (20.1%) episodes treated with frovatriptan and in 71 (23.7%) episodes treated with zolmitriptan, 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 (54.1%) and zolmitriptan (57.2%).

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 57.1% and 77.3% under frovatriptan and 58.0% and 78.8% under zolmitriptan, The between treatment difference was never statistically significant.

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. There was a statistically significant

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		

difference in recurrence between the two treatment groups in women with menstrual migraine: the rate of recurrence was lower with frovatriptan (15%) than with zolmitriptan (22%, $p<0.05$).

Other subgroup analyses

There were no clinically relevant differences in age and gender distribution in patients preferring one drug or the other.

PP Set (68 patients)

Patients with relevant preference

Of the 47 (69.1%) patients with a relevant preference, i.e. a preference value greater than +1.0 in any direction, 17 (36.2%) patients expressed preference for frovatriptan, while 30 (63.8%) patients expressed preference for zolmitriptan. 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, protracted activity 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 (24.0% and 56.9%) and zolmitriptan (31.9% and 67.2%).

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 or the frequency of recurrent episodes was never significantly different between frovatriptan and zolmitriptan, also in the PP set (recurring episodes under frovatriptan 20.1% vs. 22.5% under zolmitriptan). Also in this population cumulative hazard of recurrence at 48 hours was not significantly different between frovatriptan and zolmitriptan.

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

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		

PP results were similar to those of the FAS.

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.

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

Safety Results:

Overall, 31 AEs were reported in 21 (17.4%) patients, thereof 16 AEs in 11 (17.5%) patients during frovatriptan-zolmitriptan sequence and 15 AEs in 10 (17.2%) patients during zolmitriptan-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 zolmitriptan did.

In 7 (5.8%) patients, 13 treatment related AEs were reported, thereof 5 events in 2 (3.2%) patients under frovatriptan-zolmitriptan sequence and 8 AEs in 5 (8.6%) patients under zolmitriptan-frovatriptan sequence.

Considering treated attacks, 12 AEs under frovatriptan and 19 under zolmitriptan were recorded. 3 AEs under frovatriptan and 10 under zolmitriptan were treatment related (p=0.047). Attacks with at least one treatment related AE were 3 under frovatriptan and 5 under zolmitriptan.
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 zolmitriptan were effective in treatment of migraine. Patients were well satisfied with both medications. Safety results were in favor of frovatriptan, as shown by a significantly larger frequency of drug-related AEs under zolmitriptan. In women with menstrual

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		

migraine frovatriptan was better than zolmitriptan in reducing recurrent episodes (15% vs. 22%, $p<0.05$), ensuring a similar immediate effect of, but a a more sustained effect than zolmitriptan. This was the first direct comparative study between frovatriptan and zolmitriptan using patient preference as primary parameter, following IHS guideline indications. The concept of patient preference was shown to be valid as 82 of 107 (76.6%) 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 for its rapid activity by 77.8% of patients.This prefererence was confirmed by clincal data regarding the immediate effect of frovatriptan. Both drugs confirmed their profile, with a similar efficacy in the immediate, but frovatriptan showed lower risk of recurrence 4 to 16 hours after intake, a better tolerability profile and a better sustained effect in women with menstrual migraine, than zolmitriptan.

Date of the final report: 16 November 2010