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 not 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: Forvey®, Frovex®, Migard®, Tigreat®	Volume: Page:	
Name of active ingredient: frovatriptan		

Title:	A double-blind, cross-over patient preference study of frovatriptan versus zolmitriptan for the acute treatment of migraine
Investigators:	[redacted]
Study Centers:	Overall, 128 patients were enrolled in the study in 15 centers, thereof in 6 centers in Turkey, in 4 centers in Spain, in 3 centers in France, in 1 center in Denmark and in 1 center in Ireland, a list of study centers is provided in Appendix 16.1.4
Dates of Study:	Date of first screening: 24 Oct 2007 Date of last visit: 03 Nov 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:	128 patients (65 frovatriptan as first treatment vs. 63 zolmitriptan as first treatment)
	Safety Set:	119 patients (60 vs. 59 patients)
	Full Analysis Set (FAS):	97 patients (50 vs. 47 patients)
	Per-Protocol (PP) Set:	34 patients (14 vs. 20 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, *patients who were beneficiary of a social security regime [as per local Amendment in France dated 07 May 2007]*. 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 ≥ 7) • severe renal impairment (i.e., creatinine clearance [CrCl]	

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Name of finished product: Forvey®, Frovex®, Migard®, Tigreat®	Volume: Page:	
Name of active ingredient: frovatriptan		

	<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 • history of intolerance or inefficacy of at least two triptans for the treatment of migraine attacks • current use of 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 *and within one month after completion of this study [as per local Amendment in France dated 07 May 2007]* • inability or refusal to issue the informed consent • more than six days of tension-type headache • *vulnerable persons, i.e. persons, deprived of freedom and/or legal entity by an administrative or court order [as per local Amendment in France dated 07 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	Zolmitriptan 2.5 mg by oral route, one up to two doses per episode per day

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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 “zolmitriptan 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.

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

Summary and Conclusions:

1. Efficacy Results:

1.1 Primary Efficacy Variable

The primary efficacy variable was defined as the subjective strength 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 (97 patients)

The patient preference value was (arithmetic mean ± standard deviation [median]) 3.32 ± 0.88 [3.50] in patients preferring frovatriptan and 3.34 ± 1.12 [3.50] in patients preferring zolmitriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or zolmitriptan (p = 0.080 in ANOVA test).

1.1.2 PP Set (34 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 patient preference value was (arithmetic mean ± standard deviation [median]) 3.39 ± 0.78 [4.00] in patients preferring frovatriptan and 3.50 ± 1.03 [3.75] in patients preferring zolmitriptan. Overall, the superiority test did not show a significant preference for either frovatriptan or zolmitriptan (p = 0.075 in ANOVA test).

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Name of finished product: Forvey®, Frovex®, Migard®, Tigreat®	Volume: Page:	
Name of active ingredient: frovatriptan		

1.2 Secondary efficacy variables

1.2.1 Full Analysis Set (97 patients)

Patients with relevant preference

Of the 75 (77.3%) patients with a relevant preference, i.e. a preference value of greater than +1.0 in any direction, 31 (32.0%) patients expressed a preference for frovatriptan while 44 (45.4%) patients expressed a preference for zolmitriptan. 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=31)**	**Zolmitriptan (n=44)**
Patient preference most influential property	**n (%)**	**n (%)**
Rapid activity	12 (38.7)	14 (31.8)
Complete analgesia	7 (22.6)	8 (18.2)
Reduction of severity	3 (9.7)	10 (22.7)
Prevention of aggravation	3 (9.7)	2 (4.5)
Protracted activity	2 (6.5)	3 (6.8)
No side effects	1 (3.2)	1 (2.3)

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

The proportion of pain-free episodes under frovatriptan was 19.2% at 2 hours and 42.2% at 4 hours and under zolmitriptan 23.4% at 2 hours and 53.2% at 4 hours without statistically significant differences between the treatments.

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 1.31 ± 0.78 [1.25] points under treatment with frovatriptan and with 1.31 ± 0.76 [1.38] points under treatment with zolmitriptan. The mean overall headache intensity at 48 hours was 1.9 ± 0.9 [2.0] points under treatment with frovatriptan and 1.8 ± 0.9 [2.0] points under treatment with zolmitriptan. While in the early phase at 2 and 4 hours the headache intensity was more improved under zolmitriptan, the improvement was significantly better under frovatriptan at 24 hours thus reflecting a protracted activity of frovatriptan.

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Name of finished product: Forvey®, Frovex®, Migard®, Tigreat®	Volume: Page:	
Name of active ingredient: frovatriptan		

Secondary efficacy variables (continued)

Proportion of recurrences and time to recurrence

The proportion of patients with at least one recurring episode as well as the number of recurring episodes was lower under frovatriptan with 25 (34.2%) patients and 32 (15.3%) episodes than under treatment with zolmitriptan with 27 (39.7%) patients and 39 (19.3%) episodes without statistically significant differences between treatments. The proportion of late recurring episodes was higher under treatment with frovatriptan. Of 32 recurrent episodes under treatment with frovatriptan, 2 episodes had a time to recurrence of up to 4 hours, 19 episodes had a time to recurrence of more than 4 hours up to 24 hours and 11 episodes had a time to recurrence of more than 24 up to 48 hours. Of 39 recurrent episodes under treatment with zolmitriptan, 3 episodes had a time to recurrence of up to 4 hours, 33 episodes had a time to recurrence of more than 4 hours up to 24 hours and 3 episodes had a time to recurrence of more than 24 up to 48 hours. The median time to recurrence was 18.7 hours under treatment with frovatriptan, and 14.0 hours under treatment with zolmitriptan. In summary, there was a favorable trend for frovatriptan regarding number and time to recurrence.

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 proportion of patients and episodes with at least two medication doses within an episode were similar under treatment with frovatriptan with 77 (79.4%) patients and 161 (59.4%) episodes compared to treatment with zolmitriptan with 76 (78.4%) patients and 148 (54.8%) episodes without statistically significant differences between treatments. The proportions of patients and episodes with use of rescue medication within an episode were similar under treatment with frovatriptan with 43 (44.3%) patients and 79 (29.2%) episodes compared to treatment with zolmitriptan with 42 (43.3%) patients and 72 (26.7%) episodes without statistically significant differences between treatments.

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Name of finished product: Forvey®, Frovex®, Migard®, Tigreat®	Volume: Page:	
Name of active ingredient: frovatriptan		

Secondary efficacy variables (continued)

Sustained pain-free episodes
Under both treatments, very similar results were reported for sustained pain-free episodes after 48 hours with 36 (13.8%) episodes under treatment with frovatriptan and 33 (12.9%) episodes under treatment with zolmitriptan. As no AEs were reported during any of the sustained pain-free episodes, all AE analyses of the sustained pain-free episodes revealed identical results.

Proportion of patients requiring early cross-over or early study discontinuation
Only 2 (2.1%) patients under treatment with frovatriptan and 3 (3.1%) patients under treatment with zolmitriptan required an early cross-over or study discontinuation.

Patient's satisfaction with the treatment as recorded after 48 hours
Patients were well satisfied with both medications. The mean satisfaction (arithmetic mean ± standard deviation [median]) under treatment with frovatriptan was 2.20 ± 0.90 [2.33] points and 2.47 ± 0.98 [2.67] points under treatment with zolmitriptan ($p = 0.019$ in t- test, range from 0 = very poor to 4 = very good).

1.2.2 PP Set (34 patients)

Patients with relevant preference
Of the 25 (73.5%) patients with a relevant preference, i.e. a preference value of greater than +1.0 in any direction, 9 (26.5%) patients expressed preference for frovatriptan, while 16 (47.1%) patients expressed a preference for zolmitriptan.

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

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. 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=9)**	**Zolmitriptan (n=16)**
	n (%)	**n (%)**
Patient preference most influential property		
Rapid activity	3 (33.3)	7 (43.8)
Reduction of severity	1 (11.1)	3 (18.8)
Complete analgesia	1 (11.1)	2 (12.5)
Prevention of aggravation	2 (22.2)	0 (0.0)
Protracted activity	1 (11.1)	1 (6.3)
Recovery of functioning	0 (0.0)	1 (6.3)
Reliable activity	1 (11.1)	0 (0.0)

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

The proportion of pain-free episodes under frovatriptan was 25.0% at 2 hours and 60.8% at 4 hours and under zolmitriptan 28.0% at 2 hours and 68.4% at 4 hours without statistically significant differences between the treatments.

Change in headache intensity

Overall, the mean improvement of headache on a scale from 3 to 0 was (arithmetic mean ± standard deviation [median]) 1.57 ± 0.73 [1.50] points under treatment with frovatriptan and 1.46 ± 0.71 [1.50] points under treatment with zolmitriptan without statistically significant differences between the treatments.

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.

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.

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2. Safety Results:

Overall, 30 AEs were reported in 21 (17.6%) patients, thereof 11 AEs in 9 (8.3%) patients during treatment with frovatriptan and 19 AEs in 13 (11.8%) patients under treatment with zolmitriptan. In 10 (8.4%) patients, 15 AEs with relationship of certain, probable, possible or unlikely were reported, thereof 5 events in 5 (4.6%) patients under treatment with frovatriptan and 10 AEs in 5 (4.5%) patients under treatment with zolmitriptan. Only 3 events were reported with severe intensity, a case of abdominal pain in patient no. 118057, a pregnancy in patient 114145 and a case of intervertebral disc protrusion in patient 117063. None of the AEs with severe intensity was related to any of the study drugs. In 7 (5.9%) patients, thereof in 3 (2.8%) patients under treatment with frovatriptan and in 4 (3.6%) patients under treatment with zolmitriptan, AEs led to withdrawal, in three of these patients, pregnancy was the reason for withdrawal. One SAE, a non-related case of intervertebral disc protrusion in patient 117063 was reported under treatment with zolmitriptan. Three women experienced pregnancy during the study, however, no safety-related issues resulted from these pregnancies. No pre-treatment AEs were reported. 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.

Conclusions:

Both frovatriptan and zolmitriptan were effective in treatment of migraine as reflected by patient preference. Patients were well satisfied with both medications. Both treatments were similar with regard to frequency, distribution, intensity, relationship to study drug and outcome of AEs without clinically or statistically significant differences between the treatments. There were no relevant findings with regard to vital signs or other safety-related observations. 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 75 of 97 (77.3%) patients expressed a relevant preference and no single reason for patient preference exists. Zolmitriptan showed the same profile as in literature, while frovatriptan demonstrated an even better profile than given in the current Summary of Product Characteristics and in previous literature. Headache was significantly better under frovatriptan at 24 hours thus reflecting the long-lasting activity of frovatriptan. Moreover, under both treatments very similar results were reported for sustained pain-free episodes after 48 hours without relevant differences within the subgroups.

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