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 Sponsor: A. Menarini I.F.R. S.r.l.	Individual Trial Table Referring to Module 5.3.5.1 of the Dossier	(For National Authority Use only)
Name of Finished Product: ENANTYUM		
Name of Active Ingredient: Dexketoprofen Trometamol	Volume: Page:	

Title of Study: Dexketoprofen trometamol in the acute drug treatment of migraine attack. Phase II, randomised, double-blind, Crossover, placebo-controlled dose optimization pilot study (Study Code: MeFi/05/dex-Mig/01; EudraCT Number: 2005-000866-38)

Principal Investigator: [redacted]

Study Centre(s): Monocentric Study: 1 clinical site in Italy. [redacted]

Publication (reference): None

Study Period:	**Phase of Development**:
First patient in: 15 March 2006 Last patient out: 06 November 2008	Phase II

Objectives:

The primary objective of the study was to assess the efficacy and tolerability of two different doses of dexketoprofen trometamol (25 mg and 50 mg) in comparison with placebo in the acute treatment of migraine attack with or without aura.

The secondary objective was to compare the efficacy of the two doses of dexketoprofen trometamol in order to assess if a single 50 mg dose (two 25 mg tablets) was more effective than a single 25 mg dose in the acute treatment of migraine attack.

Trial Hypothesis:

Dexketoprofen tometamol will be superior to placebo considering the percentage of patients pain-free at 2 hours.

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Methodology:

After the signature of the informed consent, patients were screened for eligibility and eligible patients were randomised to one of the 3 groups (Group 1, Group 2, and Group 3). For each patient 3 consecutive migraine attacks were treated under double-blind with the 3 study drugs (DKP 25 mg, DKP 50 mg, and placebo) according the following treatment sequences:

	Attack 1	Attack 2	Attack 3
Group 1	DKP 25 mg	DKP 50 mg	Placebo
Group 2	Placebo	DKP 25 mg	DKP 50 mg
Group 3	DKP 50 mg	Placebo	DKP 25 mg

There was a pain-free period of at least 48 hours between each attacks, in order to avoid the treatment of a recurrence of the same attack.

Duration of Treatment:

Treatment of 3 consecutive acute migraine attacks

Number of Patients:

Planned: 90 patients (30 patients for each group)
Enrolled: 93 patients
Discontinued prior to drug intake: 15
Discontinued after 1 attack: 2 patients
Discontinued after 2 attacks: 1 patient
Major Protocol Violation: 2 patients
Minor Protocol Violation: 2 patients
ITT population (patients with at leas one evaluable attack) 76 patients
PP population (patients who completed the study): 71 patients

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Diagnosis and Main Criteria for Inclusion: Patients were enrolled in this trial with a diagnosis of mild to moderate migraine with or without aura according the Criteria of International Headache Society (IHS, 2004).

All patients had to fulfill the following eligibility criteria to participate in the trial:

- Age between 18 and 65 years
- Diagnosis of migraine since at least 1 year
- Age at migraine onset lower than 50 years
- Frequency of migraine attacks from 2 to 6 episodes/month
- Total number of day with headache per month ≤15
- Negative pregnancy test (for both pre- and peri-menopausal womren)
- Use of a highly effective method of birh control (for both pre- and peri-menopausal women)
- Written informed consent

Investigational Product and Comparator Information:

Dosage Form:

Placebo tablets

Dexketoprofen trometamol 25 mg tablets

Route of Administration:

Oral

Batch No.:

Placebo	TFG0511
Dexketoprofen trometamol:	05 18 e 07 53

Packaging Information: Medication was packaged into PVC blisters. In order to maintain blinding conditions a double-dummy technique was adopted. Each blister contained 2 tablets corresponding to the combinations *placebo + placebo*, *placebo + DKP 25 mg*, *DKP 25 mg + DKP 25 mg*. Each patient received a *patient's kit* that contained 3 blisters.

Manufacturing and packaging of the study medications were performed according GMP.

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Rescue medication: Rescue medication was prescribed by the Investigator according patient's history and preference

Criteria for Evaluation:

Efficacy:
The primary efficacy variable was the percentage of patients pain-free at 2 hours.

The secondary efficacy variables assessed were:

- Headache relief. The percentage of patients with a decrease in headache from severe or moderate to none or mild within 2 hours, before any rescue medication.
- Presence of associated symptoms. The percentage of patients with completed recovery of nausea, vomiting, photophobia and phonophobia after 2 hours, before any rescue medication
- Functional disability. Functional disability should be noted by the patient just before the drug intake and up to 2 hours later, before any rescue medication.
- Incidence of relapse (recurrence). Percentage of patients pain-free at 2 hours who experienced the return of headache of any severity within 24 hours.
- Patient's preference for treatments.
- Use of rescue medication

Safety:
The safety variables evaluated in this trial were: frequency, seriousness, and severity of adverse events (AEs), laboratory assessments of blood (clinical haematology, biochemistry) and urine (pregnancy test), vital signs (heart rate, blood pressure, physical and neurological examination).

Statistical Methods:

Interim analyses were not performed.

Main statistical hypothesis was to demonstrate that the percentage of patients pain-free at 2-h is statistically different between the 3 treatment groups (α=0.05 two tailed test).

Considering the crossover design of the study, analysis was stratified for patient and included period-effect and carry-over effect.

For both primary and secondary efficacy measures a dicotomic data analysis (logistic regression) was performed in the overall population as well as in subpopulation defined according the possible intake of rescue medications.

Analysis of variance (ANOVA) was used for the safety parameters such as heart rate, blood pressure and laboratory results in the overall population as well as in subpopulation defined according the possible intake of rescue medications. Abnormal laboratory results and adverse events were analyzed by using non

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parametric tests (Chi-square, Kruskal-Wallis, McNemar).

Summary:

Efficacy Results:

Primary outcome parameter

Patients pain-free at 2 h.

ITT Analysis

	Placebo (n=75)	DKP 25 mg (n=74)	DKP 50 mg (n=74)
Patients pain-free at 2h			
Yes	11 (14.7%)	17 (23.0%)	25 (33.8%)
No	64 (85.3%)	57 (77.0%)	49 (66.2%)
DKP 25 mg vs placebo	HR=0.483 (0.194-1.204) p=0.1182		
DKP 50 mg vs placebo	HR=0.290 (0.119-0.707) p=0.0065		
DKP 50 mg vs DKP 25 mg	HR=0.600 (0.277-1.301) p=0.1962		

N= number of attacks; HR= Hazard Ratio (95% confidence interval) p= p value

With DKP 50 mg the percentage of patients pain-free at 2 h was higher than that of placebo (33.8% vs 14.7%, p=0.0065). The corresponding value for DKP 25 mg (23.0%) was intermediate between placebo and DKP 50 mg, without statistically significant differences in comparison with both DKP 50 mg and placebo.

PP Analysis

	Placebo (n=71)	DKP 25 mg (n=71)	DKP 50 mg (n=71)
Patients pain-free at 2h			
Yes	11 (15.5%)	16 (22.5%)	23 (32.4%)
No	60 (84.5%)	55 (77.5%)	48 (67.6%)
DKP 25 mg vs placebo	HR=0.499 (0.194-1.281) p=0.1483		
DKP 50 mg vs placebo	HR=0.300 (0.118-0.760) p=0.0111		
DKP 50 mg vs DKP 25 mg	HR=0.601 (0.266-1.358) p=0.2209		

N= number of attacks; HR= Hazard Ratio (95% confidence interval) p= p value

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The results of the PP analysis were similar to those reported in the ITT, with a slightly higher percentage of patients pain-free at 2h with placebo and lower with DKP.

Secondary outcome parameters

Headache relief

ITT analysis. Patients who experienced headache relief were 25.3%, 56.8%, and 64.9% with placebo, DKP 25 mg and DKP 50 mg, respectively. The difference between DKP and placebo was statistically significant.

PP analysis. The results were similar to those reported in the ITT analysis.

Functional disability

ITT analysis. At 2 hours the percentages of patients without any disability were higher with DKP (45.9% and 39.7% with DKP 50 mg and DKP 25 mg, respectively) than with placebo (24.0%), and the difference was statistically significant.

PP analysis. The results were similar to those reported in the ITT analysis.

Effects on associated symptoms

Nausea

ITT population. The rate of complete recovery of nausea at 2 h was double with DKP (61.6% and 64.0% with DKP 25 mg and DKP 50 mg, respectively) in than that reported with placebo (33.3%). Due to the low number of patients who experienced nausea at the time of drug intake, the difference between DKP and placebo was not statistically significant.

PP analysis. The results were similar to those reported in the ITT analysis.

Vomiting

The number of patients who experienced vomiting at the time of drug intake was so low that a statistical analysis was not performed.

Photofobia

ITT population. The rate of complete recovery of photophobia at 2 h was double with DKP 25 mg (46.2%) or triple (72.3%) with DKP 50 mg than that reported with placebo (24.4.%). DKP 50 mg was statistically

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superior to placebo (p<0.0001).

PP analysis. The results were similar to those reported in the ITT analysis.

Phonofobia

ITT population. The rate of complete recovery of photophobia at 2 h was double with DKP 25 mg (52.1%) than that reported with placebo (26.5%) (p=0.0372). With DKP 50 mg the rate of complete recovery of phonophobia (43.7%) was slightly lower than that reported with DKP 25 mg, and the difference with placebo was not statistically significant.

PP analysis. The results were similar to those reported in the ITT analysis, but the difference between DKP 25 mg and placebo was not statistically significant (p=0.0551).

Incidence of relapse (recurrence)

Differences between DKP and placebo were not statistically significant in both the ITT and PP analysis.

Patient's preference

ITT analysis. The percentages of patients who would like to use the same treatment again were 72.2%, 62.2% and 37.8% with DKP 50 mg, DKP 25 mg and placebo, respectively. Differences between DKP and placebo were highly significant.

PP analysis. The results were similar to those reported in the ITT analysis.

Use of rescue medication

ITT analysis. More than two third (68%) of patients treated with placebo had to use a rescue medication for pain relief while 37.0% and 32.4% of patients had to use rescue medication with DKP 25 mg and DKP 50 mg, respectively.

Safety Results:

Overall, there were no safety issues identified during the course of this study.

Twentyeight not serious adverse events were reported in 18 patients.

At least 1 adverse event was reported every 7 attacks with placebo (9.1%), 6 attacks (7.9%) with DKP 25

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mg and every 7 attacks (9.2%) with DKP 50 mg. The differences between treatments were not statistically significant.

No clinically relevant modifications of vital signs and laboratory parameters were reported.

Conclusions:

The ITT analysis of primary endpoint (percentage of patient pain-free at 2 h) indicated that DKP 50 mg is more effective than placebo (33.8% vs 14.7%, HR 0.290 [0.119-0.707], p=0.0065) in the acute drug treatment of mild to moderate migraine attacks. DKP 25 mg had an intermediate efficacy, without statistically significant differences in comparison with both placebo and DKP 50 mg. Secondary efficacy parameters analysis confirmed the superior efficacy of DKP 50 mg.

All DKP dosage were safe and well tolerated in this study. There was no significant differences between the safety profile of DKP 50 mg, DKP 25 mg and placebo.

The higher dose (50 mg) seems the more appropriate dosage of DKP in the acute drug treatment of mild to moderate migraine attacks.

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Date of the Report: 22 September 2009