SYNOPSIS

NAME OF SPONSOR/COMPANY: JANSSEN-CILAG EMEA NAME OF FINISHED PRODUCT: Topimax®, Topamac®, Epitomax®, Topamax® NAME OF ACTIVE INGREDIENT(S): topiramate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: TOPMAT-MIG-303

EudraCT No.: 2005-000321-29

Title of Study: A double-blind, randomised, placebo-controlled, multicentre study to investigate the efficacy and tolerability of topiramate in prolonged migraine prevention.

Running Title: Prolonged migraine prevention with topiramate [PROMPT]

Investigators: International Multicentre Trial; for a list of investigators, see Appendix 1.4.1

Publication (Reference): JRF, Clinical Research Report TOPMAT-MIG-303 (EDMS-USRA-10101199:2.0)

Study Initiation/Completion Dates: 15 December 2003/ 5 May 2006 **Phase of development: III**

Objectives:

The **primary objective** of this trial was to evaluate the continued efficacy (beyond 6 months) of topiramate in the prophylaxis of migraine. The primary parameter was the change in number of migraine days (topiramate versus placebo) over the last 4 weeks in the double-blind (DB) phase relative to the last 4 weeks of the open label (OL) phase.

Secondary objectives were:

- to investigate the change in the number of migraine days, periods and attacks over the last 4 weeks of the OL phase, relative to the prospective baseline (PB) phase. In the OL phase, the distribution of preferred topiramate doses was defined for all the subjects together;
- to determine the number of responders (subjects with at least a 50% drop in the number of migraine days relative to the PB phase);
- to assess the change in the number of responders in the DB phase relative to the OL phase;
- to compare the use of acute medication (triptan, ergot, opiod and analgesic use) between placebo and topiramate, as an inverse efficacy measure of the prophylactic medication;
- to evaluate the change in quality of life assessments as compared to the PB phase and the number of drop-outs;
- to assess safety, including adverse event reporting and, if deemed necessary, blood and urine samples.

Methodology:

This was a double-blind, randomised, placebo-controlled, multicentre trial to evaluate the efficacy of topiramate in preventing migraine headaches in subjects suffering from rather frequent migraine attacks. The study was set up to evaluate the continued efficacy of topiramate after an initial 6-month open label treatment phase. To assess the effect of continued topiramate treatment versus withdrawal, half the number of the subjects was withdrawn from topiramate while the other half continued to use topiramate at the same dose for another 6 months. This was done in a randomised way, using double-blind medication.

SYNOPSIS (CONTINUED)

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Methodology, continued:

The trial had 4 consecutive phases:

Prospective Baseline (PB) phase (4 or 8 weeks):

After inclusion, subjects first entered a 4-week prospective baseline phase. No trial medication was given but migraine headaches and acute treatments were recorded in the subject's diary. If the subject did not suffer at least 4 migraine days during this 4-week period, the baseline phase was extended another 4 weeks. In that case, the total number of migraine days in the 8-week PB phase had to be at least 8.

Open Label (OL) phase (26 weeks):

Eligible subjects (those who had at least 4 monthly migraine days in the PB phase) were allowed to enter a 26-week active treatment period, the OL dose-characterisation phase. They started at a dose of 25 mg topiramate per day (evening intake). The dose was increased 25 mg/day once weekly, given as morning and evening doses. Topiramate was titrated to a target dose of 100 mg/day or maximum tolerated dose. The dose could be further adapted to the subject's need, upwards to try to raise efficacy, or downwards to try to increase tolerability, but was not allowed to exceed 200 mg/day. The final dose of topiramate had to be kept stable during at least the last 4 weeks.

Double-blind (DB) phase (26 weeks):

After having completed the OL phase, eligible subjects were allowed to enter the 26-week DB phase. Subjects were eligible if they were protocol adherent and were using topiramate at a dose of at least 50 mg/day. In the DB phase, subjects continued to use the same amount of daily tablets they took during the last 4 weeks of the OL phase, but they were randomly allocated to treatment with either topiramate or placebo in a double-blind fashion. This treatment was continued till the end of the DB phase when subjects entered the run-out (RO) phase.

Run-out (RO) phase (0-1 week):

After having completed the DB phase, or after early withdrawal, the use of trial medication was discontinued. Subjects tapered their medication at a rate of 100 mg/day once weekly. Depending on the dose, they needed to return for the final visit 1 week later. For subjects who were using a final topiramate dose of 100 mg/day or less (or corresponding placebo), the final visit coincided with the last visit of the DB phase. During the RO phase, blinding of the trial medication was fully maintained.

Number of Subjects:

Based on the results of the 3 former randomised, controlled studies with topiramate in migraine prophylaxis the following assumptions were made:

- it was anticipated that at the end of the DB phase the difference between the two groups would be 1.0 migraine day per month;
- estimated standard deviation of the change in the number of migraine days (average of the numbers found in previous trials) would be 2.5.

Under these assumptions two treatment groups of 142 subjects each were needed in the DB phase to show a statistically significant difference between topiramate and placebo with a power of 0.90 and alpha=0.05 (two-sided).

SYNOPSIS (continued)

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Number of Subjects, continued:

For this trial it was assumed that the number of subjects entered in the trial would be reduced by 25% due to screening failures (PB phase), 35% due to drop-outs (in OL phase), 20% due to discontinuation between OL phase and start of DB phase. This implied that 730 subjects needed to be included in the trial.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria

Subjects who met all of the following criteria were eligible for this trial:

1. between 18 and 80 years of age inclusive;
2. fulfilled the IHS criteria for migraine;
3. established history of migraine for at least one year;
4. an average of at least 4 monthly migraine days during the 3 months preceding trial entry;
5. capable of keeping trial records;
6. signed and dated the Informed Consent Form (ICF).

Inclusion criteria for entering the Open Label Phase:

1. at least 4 migraine days during the 4-week prospective baseline (PB) or, if this phase was extended, at least 8 migraine days during the 8-week PB phase;
2. not pregnant (for women of childbearing potential, this had to be evidenced by a negative pregnancy test).

Inclusion criteria for entering the Double-Blind Phase:

1. daily dose of topiramate had been stable during the last 4 weeks of the OL phase (Weeks 23-26);
2. daily dose of topiramate was at least 50 mg (2 tablets) and at most 200 mg during the last 4 weeks of the OL phase.

Test Product: topiramate

Dose:

***OL phase*:** after starting with one daily evening dose of 25 mg for one week, the dose was titrated using weekly 25 mg/day increments up to a target dose of 100 mg/day at Week 4. After reaching the target dose, further titration to individualised optimal dose (with 25 mg/day once a week) with a maximum allowed dose of 200 mg/day. Dose should be kept stable during the last 4 weeks of the OL phase. A range of 50-200 mg daily had to be respected.

DB phase: number of tablets taken at the end of OL phase is continued during DB phase; the number of tablets was not allowed to be increased or decreased (max. 1 tablet/day more or less allowed). Switch from OL treatment to placebo was achieved in a double-blind fashion at a rate of 100 mg/day once weekly.

***RO phase*:** dose was tapered off using 100 mg/day once weekly decrements such that complete discontinuation was achieved at the final visit.

SYNOPSIS (continued)

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Mode of Administration: oral tablets containing either 25mg topiramate, or matching placebo. Treatment was started in the open-label phase with 1 topiramate tablet in the evening. The dose was titrated up by 1 tablet/day, once a week, until the target dose of 4 tablets/day or maximum tolerated dose was reached. Tablets were given twice daily (morning and evening dose), the dose was not allowed to exceed 8 tablets per day (equivalent to topiramate 200 mg/day).

Batch No.:

Topiramate tablets for open-label treatment: batches V03PK8652, V03PK8653, V03PK8654, V04PE8850, V04PJ8985, V04PJ8986, V04PL9079, V04PL9080.
Topiramate tablets for double-blind treatment: batches P0400973, V04PD8810, V04PD8811.

Placebo tablets for double-blind treatment: batches D03LK1145, V04PD8809, V04PD8812.

Duration of Treatment: 6 months treatment in OL followed by 6 months treatment in DB. Tapering-off during 1 week RO phase.

Criteria for Evaluation:

Efficacy:

Primary efficacy criterion: change in the number of migraine days (topiramate versus placebo) during the last 4 weeks of the DB phase relative to the last 4 weeks of the OL phase.

Secondary efficacy criteria:

- change in the monthly number of migraine periods, attacks, headaches
- change in the duration and severity of migraine headaches
- responder rate (subjects with at least 50% drop in the number of migraine days)
- change in the number of days with acute medication intake
- health-related quality of life questionnaires (SF-12, HIT-6 and MIDAS)
- subject satisfaction

Safety/tolerability:

- AE reporting
- clinical laboratory tests
- vital signs
- body weight and BMI

Statistical Methods: Descriptive statistics, Wilcoxon two-sample test, Wilcoxon signed-rank test, Fisher's exact test. Cut-off level for statistical significance was set at $p<0.05$. All comparisons were 2-sided.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

STUDY POPULATION:

This trial enrolled 818 subjects who were treated for 26-weeks (or until premature discontinuation) with topiramate in an open label fashion. Following completion of the OL phase, 514 subjects were randomised to subsequent double-blind treatment with either topiramate or placebo. Four hundred seventeen (417) subjects completed also the 6-month double-blind period of the trial. Treatment compliance was high throughout both phases.

The trial population consisted predominantly of females (87%) with a median age of 40 years. Their mean number of monthly migraine days at baseline was 8.9 (SD 4.3) days expressed as a 28-day rate.

At the start of the trial, demographic parameters and severity of the disease were similar between treatment groups.

EFFICACY:

Primary efficacy endpoint: Change in the number of monthly migraine days:

Phase and treatment	Actual number at start of the phase (baseline)	Actual number during last 28 days in the phase	Change from baseline in the phase
Open label phase, topiramate treatment (N=812)			
n	811	811	811
Mean (SD)	8.93 (4.29)	5.83 (4.89)	-3.09 (5.12)
Median	8.0	5.0	-3.2
Range	0.0; 28.0	0.0; 28.0	-28.0; 23.2
p-value (change from baseline)[a]	-	-	<0.0001
Double-blind phase, topiramate treatment (N=254)			
n	253	253	253
Mean (SD)	4.87 (3.66)	4.97 (3.85)	**0.10** (3.70)
Median	5.0	4.0	0.0
Range	0.0; 18.0	0.0; 20.0	-15.0; 13.0
p-value (change from baseline)[a]	-	-	0.5756
Double-blind phase, placebo treatment (N=258)			
n	257	257	257
Mean (SD)	4.63 (4.03)	5.82 (4.36)	**1.19** (3.91)
Median	4.0	5.0	1.0
Range	0.0; 28.0	0.0; 28.0	-16.0; 17.0
p-value (change from baseline)[a]	-	-	<0.001
p-value (difference between treatments)[b]	-	-	**0.0011**

[a] Within group change from baseline using Wilcoxon signed-rank test, 2-tailed
[b] Difference in efficacy with topiramate treatment using Wilcoxon two-sample test, 2-tailed
N = number of subjects per treatment group; n = number of subjects with data

Initial treatment with topiramate in the OL phase, for the time that subjects were treated with topiramate in the OL phase, resulted in highly statistically significant improvement in the number of monthly migraine days with on average 3.1 migraine days per 4 weeks (endpoint analysis) or 4.0 migraine days per 4 weeks for subjects who completed the 26-week topiramate OL treatment phase (p<0.001).

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SUMMARY – CONCLUSIONS, CONT'd

Subsequent to the OL phase, randomisation to continued topiramate or placebo treatment, resulted in the following changes relative to DB baseline:

- No statistically significant change from DB baseline to the last 28 days in the DB phase was observed with regard to the number of monthly migraine days for subjects who remained on topiramate treatment.

- A statistically significant increase from DB baseline in the average number of migraine days per 4 weeks (from 4.63 to 5.82) was noted in subjects randomised to placebo treatment ($p<0.001$).

- The change in the number of monthly migraine days, observed in the last 28 days of the DB period as compared to the last 28 days of te OL period (primary endpoint) was statistically significantly larger in the placebo group (+1.19 days) than in the topiramate group (+0.10 days), i.e., $p=0.0011$ beween groups.

Secondary efficacy endpoints

Improvement in migraine condition throughout the OL phase was also apparent from statistically significant changes in the majority of secondary parameters, i.e.,

- The mean number of monthly migraine periods decreased from 8.20 to 5.47, corresponding to an average decrease of 2.73 migraine periods per 4 weeks; the mean number of monthly migraine attacks decreased statistically significantly from 5.95 to 3.99, an average decrease of 1.96 migraine attacks per 4 weeks;

- Severity of the migraine headaches, as rated on a scale from 1 to 3, decreased from 2.14 to 2.02;

- The mean number of monthly auras decreased from 1.00 to 0.55 for all subjects, and from 3.01 to 1.66 for those who had auras (33% of all subjects).

- The mean number of days with acute medication decreased from 6.11 to 4.16 days, respectively, corresponding to a change of -1.95 days with intake;

- HIT-6 total score, MIDAS total score, and SF-12 physical and mental component summary scores indicated improvement in the subjects' quality of life.

- Mean migraine headache duration remained unchanged throughout the OL phase (13.2 hours per headache at the start and end of the OL phase).

- Similar to the changes in number of migraine days, observations of slight but statistically significant deteriorations relative to DB baseline in the placebo group and of maintenance of efficacy in the topiramate group were also made for the number of migraine periods and attacks, severity of migraine headaches, acute medication intake, and MIDAS score. The number of auras, the changes in HIT-6 score, and the duration of migraine headaches, on the other hand, did not change significantly from DB baseline.

- Over the entire duration of the trial, within-group decrease from OL baseline in the number of monthly migraine days was statistically significant. This was true for both DB treatment groups (placebo and topiramate). Six-month DB placebo treatment following 6-month OL topiramate treatment was not statistically significantly different from continued topiramate treatment over a period of 12 months, suggesting a persistent benefit of the initial 6-month topiramate treatment over a longer period of time, even after its discontinuation.

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SUMMARY – CONCLUSIONS, CONT'd

SAFETY/TOLERABILITY RESULTS:

Adverse events (AEs)

The most commonly reported treatment-emergent adverse event (TEAE) during both phases of the trial was paraesthesia, reported in 50% of subjects in the OL phase and in 30% and 21% of subjects during topiramate and placebo treatment, respectively, in the DB phase. Other frequently reported TEAEs during OL treatment were fatigue (12%), disturbance in attention (12%), and anorexia/decreased appetite (11%). Other frequently reported TEAEs during DB treatment were decreased weight (9% of topiramate-treated subjects) and fatigue (7% of topiramate-treated subjects).

There were no deaths during the trial and the incidence of serious adverse events and adverse events leading to study drug discontinuation was relatively low.

	OL phase All subjects (N=818)	DB phase Topiramate (N=254)	DB phase Placebo (N=258)
No. of subjects with at least one TEAE (%)	695 (85)	173 (68)[a]	151 (59)[a]
No. of subjects with at least one serious TEAE (%)	22 (3)	7 (3)	10 (4)
No. of severe TEAEs (%)	290 (9)	34 (7)	19 (4)
No. of TEAEs leading to permanent stop (%)	352 (13)	16 (3)	13 (3)
No. of TEAEs at least possibly related to trial medication (%)	1953 (74)	252 (53)	223 (49)

[a] prevailing during DB phase, i.e., started during DB or started during OL and ongoing during DB

Clinical Laboratory tests:

Laboratory test results indicated a statistically significant reduction in bicarbonate levels and a statistically significant increase in chloride levels during the course of the OL treatment. At OL endpoint 39% of subjects had treatment-emergent above normal chloride, and 40% had below normal bicarbonate levels. Changes in potassium (small decrease) and sodium (small increase) levels were also seen during OL treatment. Although statistically significant, the clinical relevance of these small changes is doubtful.

Vital signs:

Reductions in SBP, DBP, and heart rate during topiramate treatment were small but nevertheless statistically significant during the OL phase. There was a slight but statistically significant increase in SBP and DBP in the placebo group but not in the topiramate group during the DB phase. Difference in change over the DB phase between treatment groups was statistically significant for both SBP and DBP.

Body Weight:

Body weight decreased statistically significantly during OL topiramate treatment, by on average 3.0 kg. During DB topiramate treatment, body weight showed a further slight decrease, whereas there was a statistically significant increase in body weight for those treated with DB placebo. Difference between the treatment groups was statistically significant at all timepoints in the DB phase.

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CONCLUSION:

Transfer of subjects, after the initial 26-week topiramate treatment, to 26-week placebo treatment resulted in significant deteriorations with regard to migraine condition, while 26-week continued topiramate treatment resulted in maintenance of efficacy. Nevertheless, 6-month placebo treatment following 6-month topiramate treatment was not statistically significantly different from continued topiramate treatment over a period of 12 months. This suggests a persistent benefit of topiramate over a longer period of time, even after its discontinuation.

Besides the recognised safety pattern of topiramate, no new or additional safety-related information emerged in this trial.

Date of the Clinical Study Report: Final - 07 July 2007

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