Janssen Research & Development

Clinical Study Report Synopsis
[Protocol TOPMAT-MIG-201; Phase 2]

RWJ-17021-000 (Topiramate)

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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-201

EudraCT No.: 2005-000320-17

Title of Study: A Randomized Double-Blind Placebo Controlled Trial to Investigate the Efficacy and Tolerability of Topiramate in the Prophylaxis of Chronic Migraine.

Running Title: Topiramate in Chronic Migraine [TOP CHROME]

Principal Investigators:

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Publication (Reference): JRF, Clinical Research Report TOPMAT-MIG-201 (EDMS-USRA-9780750:2.0)

Study Initiation/Completion Dates: 10-NOV-2003/14-JUL-2005 **Phase of development:** 2

Objectives: The primary objective of this trial was to investigate the effectiveness of topiramate in preventing migraine headaches in subjects with chronic migraine. The primary efficacy analysis was based on the change versus baseline in the number of migraine days during the last 4 weeks of the double-blind treatment phase in the topiramate group as compared to the placebo group.

The target dose for topiramate was set at 100 mg/day but dosages between 50 and 200 mg/day were allowed, so the trial could provide the preferred dose distribution in subjects with chronic migraine.

Stratification for acute medication overuse was applied to enable separate analyses for subjects with and without medication overuse.

In addition to the frequency of migraine days, the duration and severity of the migraines were analyzed. Indirect parameters for efficacy were the change in the days with acute medication use, the change in the quality of life assessments, and the subject satisfaction score.

Adverse events were recorded to assess the safety and tolerability of flexible doses of topiramate.

Methodology: This was a randomized, double-blind, placebo controlled, parallel-group, multi-center trial to evaluate the efficacy and tolerability of topiramate in preventing migraine headaches in subjects with chronic migraine.
Sixty subjects had to be randomized equally to either topiramate or placebo treatment, randomization was stratified per center and according to the presence or absence of medication overuse. Subjects were given a diary for the appropriate record keeping of their migraines and any acute treatment they took to treat those migraines.

SYNOPSIS (CONTINUED)

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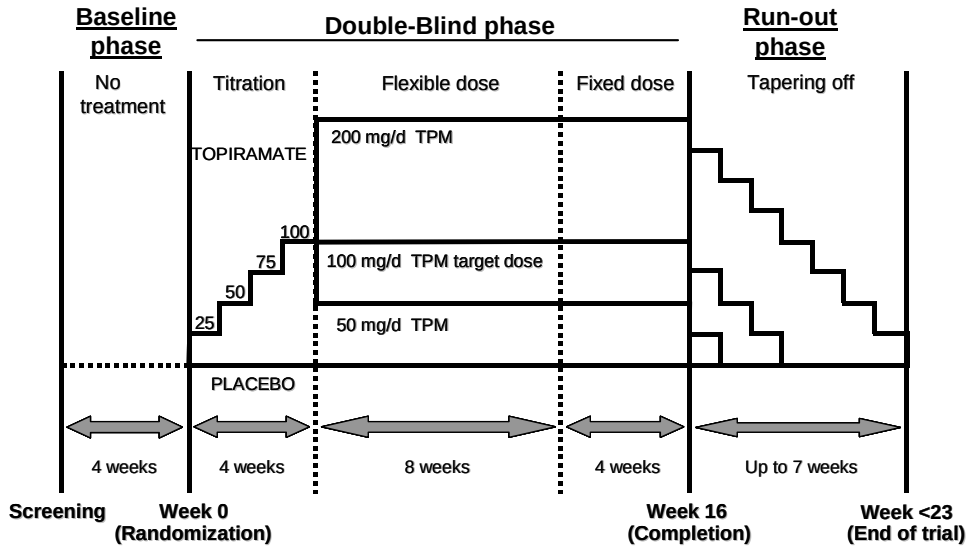
Methodology, continued:

The trial had 3 successive phases.

- After inclusion subjects first entered a 4-week prospective baseline phase. No trial medication was given in this phase but migraine headaches and acute treatments needed to be recorded in the subject's diary.
- Eligible subjects were then allowed to enter the 16-week core double-blind phase. They received double-blind medication containing either topiramate (TPM) or placebo. Trial medication was titrated to an initial target dose of 100mg/day or the maximum tolerated dose. The dose could be further adapted to the subject's need. This had to be completed in Week 12 since the final dose had to be kept stable during the last 4 weeks of the double-blind phase.
- In the double-blind run-out phase thereafter, the dose of the medication was gradually reduced using 25 mg/day (or corresponding placebo) weekly decrements such that complete discontinuation was achieved at the final visit. Migraine headaches were not recorded anymore during the run-out phase.

In the double-blind phase topiramate was started at a dose of 25 mg in the evening, and titrated with 25 mg/day increments once weekly (given as morning and evening doses) until an initial target dose of 100 mg/day was reached. Dose adjustments were allowed for tolerability or efficacy reasons and were guided by the subject's experiences. This was of particular importance in the early titration phase when the investigator and the subject had telephone contact in between the scheduled visits, i.e. at Week 2 and Week 6 of the double-blind phase. Dose adjustments were allowed to a maximum dose of 200 mg/day and to a minimum dose of 50 mg/day. The final dose had to be kept stable at least during the last 4 weeks of the 16-week double-blind phase.



Randomization was stratified according to presence/absence of medication overuse and study center.

SYNOPSIS (CONTINUED)

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Number of Subjects: Based on previously obtained data in episodic migraine, the original estimation of the primary effect size was that the reduction in migraine days would be 45% on topiramate versus 25% on placebo. With an expected average of 20 migraine days per month and an estimated standard deviation of the change in migraine days per month of 5, the sample-size calculation indicated that at least 29 subjects per treatment group were needed to show a statistically significant difference between treatment groups (power: 0.80, alpha: 0.05, two-sided). The target was therefore set at 60 randomized subjects. In the trial 82 subjects were screened in the prospective baseline phase. There were 23 screen failures, 59 subjects were eventually randomized.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria

1. Subject was between 18 and 65 years of age inclusive.
2. Subject had migraine according to the IHS criteria (Addendum 1).
3. Subject had an established history of migraine for at least one year.
4. Subject had chronic migraine, which means having a migraine headache on 15 or more days per 4 weeks. This requirement had to be fulfilled during at least the last 3 months prior to trial entry.
5. Subject was otherwise healthy on the basis of medical history and a pre-trial physical and neurological examination.
6. Subject was capable of keeping trial records.
7. Subject (or subject's legally acceptable representative) had signed and dated the Informed Consent Form (ICF).

Additional selection criteria applied at the start of the double-blind phase were:

- Subject had at least 12 days with migraine headache per 4 weeks during the baseline phase.
- If subject was female and of child-bearing age, absence of pregnancy was evidenced by a negative pregnancy test.

Exclusion criteria

1. Subject had another primary chronic headache from section 2 to13 of the IHS classification, or any secondary headache except medication overuse headache.
2. Onset of migraine after age 50.
3. Use of an anticonvulsant drug in the 30 days prior to trial entry.
4. Use of an antidepressant drug, unless the antidepressant was being used at a stable dose for at least 3 months prior to trial entry and was going to be continued throughout the trial.
5. Use of a migraine prophylactic drug, unless the drug was being used for at least 3 months, its dose was stable for at least 1 month, and its use was going to be continued throughout the trial.
6. Use of a carbonic anhydrase inhibitor, such as acetazolamide, or triamterene.
7. Prior use of topiramate.
8. Subject was not suitable for topiramate according to marketed contraindications in the country in which the subject was being studied.
9. Subject participated in an investigational drug trial in the 30 days prior to trial entry.

SYNOPSIS (CONTINUED)

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Exclusion criteria, cont'd

10. History of severe drug allergy or hypersensitivity.
11. History or suspicion of alcohol or drug abuse, e.g., use of barbiturates, amphetamines, ecstacy, cannabis, or narcotics.
12. Subject was pregnant or breastfeeding female. For women of childbearing age, absence of pregnancy had to be confirmed by negative HCG test/serum β-HCG at trial entry.
13. Subject was female and of childbearing potential without adequate contraception. Adequate contraception was defined as use of contraceptive medication or intrauterine device, bilateral tubal ligation, or appropriate non-hormonal contraceptive practice. Women who had a total hysterectomy or were 2 years post menopausal needed not be excluded.
14. Severely depressed mood (Beck Depression Inventory ≥ 30).
15. History of nephrolithiasis.
16. Serious illnesses: liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, psychiatric, or metabolic disturbances.
17. Subject was an employee of the investigator or the institution who was directly involved in the trial or other trials under the direction of the investigator or the institution's members.

Test Product: topiramate

Dose: During double-blind phase: titration using weekly 25 mg/day increments to a target dose of 100 mg/day. First 12 weeks, range: 50-200 mg/day, last 4 weeks, dose had to be kept stable.
During run-out phase: dose was tapered off gradually using 25 mg/day weekly decrements such that complete discontinuation was achieved at the final visit.

Mode of Administration: oral tablets

Batch No.: First medication set: Packaging Lot number: P03-00726/P03-00754
Topiramate: Manufacturing Lot number: D00LM0570
Bulk Lot number: V03PF8485
Matching placebo: Manufacturing Lot number: D00LH0506
Bulk Lot number: V03PF8486
Replacement medication: Packaging Lot number: P04-01109
Topiramate: Manufacturing Lot number: D04PC7346 (3KG0866)
Bulk Lot number: V04PG8923
Matching placebo: Manufacturing Lot number: D04PC7347 (PD1104)
Bulk Lot number: V04PG8924

Duration of Treatment: 16 weeks, excluding 4-week prospective baseline phase, and run-out phase (maximum: 7 weeks)

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Efficacy:

Primary efficacy criterion: change in the number of migraine days (topiramate versus placebo) from the 4-week prospective baseline phase to the last 4 weeks of the double-blind phase.

Secondary efficacy criteria:

- monthly number of migraine periods, attacks, headaches at the various visits in the double-blind phase
- monthly number of migraine days, periods and attacks over the entire double-blind phase
- duration and severity of migraine headaches
- responder rate
- intake of acute medication
- health-related quality of life questionnaires (MSQ, HIT-6 and MIDAS)
- subject satisfaction

Safety/tolerability:

- AE reporting
- clinical laboratory tests: biochemistry, hematology and urinalysis
- 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. No corrections were made for multiplicity of comparisons.

SYNOPSIS (CONTINUED)

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SUMMARY - CONCLUSIONS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

		Topiramate (N = 32)	**Placebo (N = 27)**
Sex, n(%)	Male Female	8 (25) 24 (75)	7 (26) 20 (74)
Age (years)	Mean Median (range)	47.8 50 (25; 63)	44.4 45 (25; 65)
Height (cm)	Mean Median (range)	165.8 165 (147; 191)	165.6 164 (150; 185)
Weight (kg)	Mean Median (range)	70.4 67 (51; 135)	67.9 64 (49; 98)
BMI (kg/m²)	Mean Median (range)	25.4 23.4 (19.5; 37.0)	24.7 23.7 (18.7; 35.8)
Beck Depression Inventory (BDI)	Mean Median (range)	9.0 9 (0; 29)	13.4 11 (1; 30)
Migraine Days (baseline)	Mean Median (range)	15.5 15.0 (9.3; 27.0) *	16.4 16.4 (8.9; 27.0) *
Medication Overuse, n (%)	At trial start During baseline	23 (72) 20 (63)	23 (85) 18 (67)

* 8 subjects in the topiramate group and 5 in the placebo group had less than 12 migraine days at baseline.

EXTENT OF EXPOSURE:

		Topiramate (N = 32)	**Placebo[a] (N = 27)**	**Topiramate versus Placebo (p-value[b])**
Number of days in the DB phase:	Mean (SD) Median Range	101.8 (29.4) 114 29; 140	95.7 (31.2) 108 13; 139	0.3893
Number of days with dosing:	Mean (SD) Median Range	99.7 (30.5) 112 29; 140	92.3 (35.3) 108 12; 139	0.4980
Last daily dose (mg/day):	Mean (SD) Median Range	106.3 (26.9) 100 50-200	125.0 (47.0) 100 50-200	0.0934
Mode daily dose (mg/day):	Mean (SD) Median Range	100.0 (16.8) 100 50; 150	118.5 (49.3) 100 25; 200	**0.0364**

[a] For trial medication dosing: tablet use in the placebo group is also indicated in mg/day, as if topiramate had been given.
[b] Between group comparison by Wilcoxon two sample test, 2-tailed.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS, CONT'd

EFFICACY RESULTS:

Primary efficacy endpoint

Number of migraine days per 4 weeks		**Topiramate (N = 32)**	**Placebo (N = 27)**	**Topiramate versus Placebo (p-value[b])**
During prospective baseline phase	Mean (SD) Median Range	15.53 (4.60) 15.0 9.3; 27.0	16.42 (4.37) 16.4 8.9; 27.0	0.2832
During last 4 weeks of double-blind phase	Mean (SD) Median Range	12.06 (6.53) 10.5 1.0; 28.0	16.66 (5.87) 16.0 7.0; 27.0	**0.0053**
Change	Mean (SD) Median Range p-value[a]	-3.47 (6.26) -3.0 -21.0; 9.0 **0.0027**	0.24 (4.74) 0.0 -8.3; 8.1 0.8051	**0.0203**

[a] Within group comparison by Wilcoxon signed rank test, 2-tailed.
[b] Between group comparison by Wilcoxon two sample test, 2-tailed.
Bold: Statistically significant changes ($p < 0.05$) are indicated in bold.

Secondary efficacy endpoints

Secondary efficacy analysis during the complete double-blind treatment phase revealed a statistically significantly higher reduction in the number of migraine headaches, days, periods and attacks at virtually all time points during the double-blind treatment phase under topiramate compared to placebo treatment.

Changes in duration as well as severity of migraine headaches were only minor and not statistically significant either within or between both treatment groups.

Fifty percent response rate to therapy based on the change in number of migraine days was statistically significantly higher under topiramate (22-29%) compared to placebo (0-4%) treatment during most of the double-blind phase. Conclusions for the responder rates based on migraine periods (instead of days) are the same, whereas the responder rates based on migraine attacks are somewhat less pronounced and therefore not as statistically significant as the numbers for migraine days and periods.

The study was not adequately powered to demonstrate statistical significance of the changes found with the three health-related quality of life questionnaires, i.e., MSQ, HIT-6 and MIDAS.

MSQ score for "Role Function-Restrictive" was nevertheless statistically significantly improved relative to baseline at all assessments in both treatment groups. In the topiramate group only, changes in MSQ scores for "Role Function-Preventive" and for "Emotional Function" were also statistically significant relative to baseline at all assessments. The apparently greater improvement in the topiramate group for the latter 2 dimensions, however, did not reach statistical significance when compared to the improvements in the placebo group.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS, CONT'd

Secondary efficacy endpoints, cont'd

HIT-6 scores improved in a statistically significantly manner relative to baseline at all assessments of the double-blind phase, but it did so in both treatment groups and without any statistically significant difference between the treatment groups.

MIDAS scores were statistically significantly improved relative to baseline at the end of the double-blind phase in the topiramate group, but not in the placebo group. The between group comparison of the change in MIDAS score also revealed a statistically significantly better improvement under topiramate compared to placebo treatment.

Subject satisfaction with the effectiveness of the trial medication was statistically significantly higher under topiramate compared to placebo treatment. No statistically significant difference was observed in subject satisfaction with the tolerability of the trial medication between topiramate and placebo treated subjects.

Subgroup analysis of the subjects with medication overuse (topiramate/placebo: 23/23) yielded results similar to the overall analysis, with also a statistically significant primary efficacy parameter: the mean change in the number of migraine days per 4 weeks was -3.49 and +0.82 for topiramate and placebo treated subjects, respectively (p=0.027). Due to the limited number of subjects without medication overuse (topiramate/placebo: 9/4) a separate analysis of this subgroup was not performed. The per-protocol analysis (topiramate/placebo: 24/19 subjects) yielded results that were qualitatively similar to those of the main analysis but often lacked statistical significance, most probably due to a lack of statistical power.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS, CONT'd

SAFETY/TOLERABILITY RESULTS:

Adverse events (AEs)

	Topiramate	**Placebo**	**Total**
Number of subjects with AE, n (%)	**32 (100)**	**27 (100)**	**59 (100)**
At least one AE	25 (78)	10 (37)	35 (59)
At least one TEAE	24 (75)	10 (37)	34 (58)
At least one SAE	1 (3)	1 (4)	2 (3)
An AE that caused death	0	0	0
At least one AE for which study medication was permanently stopped	6 (19)	3 (11)	9 (15)
Number of AEs, n (%)	**74 (100)**	**18 (100)**	**92 (100)**
Serious AE (SAE)	1 (1)	1 (6)	2 (2)
Severe AE*	23 (32)	8 (44)	31 (34)
AE for which study medication was permanently stopped	9 (12)	4 (22)	13 (14)
AE for which study medication was temporarily stopped	1 (1)	0	1 (1)
AE for which dose of study medication was adjusted	3 (4)	0	3 (3)
AE for which concomitant medication was started	16 (22)	8 (44)	24 (26)
Possibly drug related AE	23 (31)	5 (28)	28 (30)
Probably drug related AE	6 (8)	1 (6)	7 (8)
Very likely drug related AE	9 (12)	3 (17)	12 (13)
Possibly, probably or very likely drug related AE	38 (51)	9 (50)	47 (52)
AE from which subject had not yet recovered at trial end	9 (12)	5 (28)	14 (15)

TEAE: treatment-emergent adverse event.
*: number of AEs with missing severity = 1.

SYNOPSIS (CONTINUED)

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Treatment-emergent adverse events with incidence ≥ 2 subjects:

Number (%) of subjects with TEAE	**Topiramate (N = 32)**	**Placebo (N = 27)**
Any TEAE	**24 (75)**	**10 (37)**
Paresthesia	17 (53)	2 (7)
Nausea	3 (9)	0
Anorexia	2 (6)	1 (4)
Disturbance in attention	2 (6)	1 (4)
Dizziness	2 (6)	0
Dyspepsia	2 (6)	0
Fatigue	2 (6)	0
Influenza-like illness	1 (3)	1 (4)
Memory impairment	1 (3)	1 (4)
Somnolence	1 (3)	1 (4)
Vomiting	1 (3)	1 (4)

Clinical Laboratory tests:

No laboratory abnormalities were found except for a small rise in serum chloride levels (+3.9 mmol/L) in the topiramate group that was also statistically significant compared to the placebo group. A rise in chloride levels under topiramate treatment has been reported before, and is believed to result from its carbonic anhydrase inhibitory properties. No clinical laboratory abnormalities were reported as AE.

Vital signs:

There were no statistically significant changes from baseline in vital sign parameters.

Body Weight:

Body weight was statistically significantly reduced under topiramate treatment compared to baseline at all assessments, and compared to placebo treatment at Week 8 and at the end of the double-blind treatment phase. Weight reduction is known to occur frequently as a side effect of topiramate treatment.

CONCLUSION:

When administered at a flexible dosing from 50-200 mg/day, topiramate was effective in the prevention of migraine headaches in subjects with chronic migraine with or without acute medication overuse. Topiramate was generally safe and well tolerated.

Date of the Clinical Study Report: 29 September 2006