Title page

CLINICAL STUDY REPORT

SAFETY AND EFFICACY OF A NOVEL MODIFIED RELEASE FORMULATION OF OXCARBAZEPINE (OXC MR) VS AN IMMEDIATE RELEASE OXCARBAZEPINE (OXC IR) PRODUCT IN PATIENTS WITH PARTIAL EPILEPSY - OPEN-LABELLED, CONTROLLED, PARALLEL GROUP, FLEXIBLE- DOSE, MULTICENTER STUDY

OXC-039/K

EudraCT No.: 2006-003834-14

Investigational product:	oxcarbazepine modified release
Clinical development phase:	3
Sponsor:	Desitin Arzneimittel GmbH Weg beim Jäger 214 22335 Hamburg, Germany
Coordinating Investigator:	Prof. Dr. med. C. E. Elger Klinik für Epileptologie Sigmund-Freud-Strasse 25 53127 Bonn, Germany
Date of first patient enrolled:	23-Oct-2006
Date of last patient completed:	24-Nov-2009
Early termination:	Yes, 01-Apr-2010
Persons responsible for study report:	Dr. K. Kuhn and Dr. M. Wangemann Desitin Arzneimittel GmbH Weg beim Jäger 214 22335 Hamburg, Germany
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Report version and date:	Final 1.0 (02-Dec-2010)

This study was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents.

The signature of the Coordinating Investigator and the Sponsor's Signatories are available in Appendix 16.1.5.

1 Synopsis

Title of the study:
Safety and efficacy of a novel modified release formulation of oxcarbazepine (OXC MR) vs an immediate release oxcarbazepine (OXC IR) product in patients with partial epilepsy - Open-labelled, controlled, parallel group, flexible-dose, multicenter study.

Principal Investigator(s) and study center(s):
A total of seven Investigators at six study centers in Germany.

Coordinating Investigator: Prof. Dr med. C E Elger, Klinik für Epileptologie, Sigmund-Freud-Strasse 25, 53127 Bonn, Germany.

Publication (reference): Not applicable.

Studied period: 23-Oct-2006 (first patient in) to 24-Nov-2009 (last patient out).

Premature termination: 01-Apr-2010

Clinical phase: phase 3

Objectives:
Primary objective: To evaluate the maintenance dose where dose up-titration had to be discontinued due to adverse events.

Secondary objectives:

- To evaluate the AE profile, and course of performance and cognition, during up-titration to a maximum dose of 2,700 mg/day with OXC MR in comparison with OXC IR by means of a validated Adverse Event Profile Plus (AEP Plus) questionnaire and the EpiTrack test protocol.
- To compare both groups on the criteria seizure frequency per 28 days.
- To compare plasma concentrations of OXC and the S- and R- enantiomers of 10-monohydroxy derivative (MHD) obtained before the morning dose and 1 to 3 hours after drug intake (immediately after AEP Plus and the EpiTrack test, n = 6 patients/center).

Methodology:
This was a multi-center, randomized, open-label, flexible-titration, controlled, parallel-group study to investigate the safety and efficacy of OXC MR compared to an OXC IR product in patients with partial epilepsy.

During a 4-week baseline period patients recorded the number of seizures and the number of tablets of OXC IR taken. Patients who met the entry criteria were randomized in a

1:1 randomization to receive either OXC MR twice daily (b.i.d.) or OXC IR b.i.d. for 26 weeks. Study Visits were scheduled at Day 1 (Visit 1), Day 16 (Visit 2), and Day 26 (Final Visit). Telephone calls (TC) were made on Days 6, 11, and 21. At Visit 1 (Study Day 1) the patients received a total daily dose of 1,200 mg, 1,500 mg, or 1,800 mg OXC. From Day 6 the dose was up-titrated in steps of 300 mg every 5th day to a maximum total daily dose of 2,700 mg. Patients who experienced intolerable AEs reduced their daily dose by 150 mg on the 2nd day of up-titration and maintained this dose for the remainder of the treatment period. If the reduced dose was not tolerated, the dose was further reduced by 150 mg of OXC. The maximum tolerated dose was maintained up to the Final Visit (Study Day 26). A prespecified interim analysis was performed once 40 patients had completed at least one round of up-titration.

Blood samples were taken prior to and between 1 and 3 hours after dosing to measure plasma levels OXC and S- and R-MHD. The samples were taken from 6 patients per center at Visit 1, Visit 2, and the Final Visit.

Number of patients (total and for each treatment) planned and analyzed:

- According to protocol: 100 patients
- The study was stopped prematurely due to insufficient patient recruitment
- Analyzed sets:

	Enrolled and randomized (N)	SAF (N)	ITT (N)	PP (N)
After interim analysis				
OXC MR	15	n.a.	15	7
OXC IR	16	n.a.	16	10
Total	31	n.a.	31	17
All patients				
OXC MR	35	35	35	22
OXC IR	36	36	36	19
Total	71	71	71	41

IR = immediate release, ITT = intention-to-treat analysis set, MR = modified release, N = number of patients, n.a. = not applicable, OXC = oxcarbazepine, PP = per-protocol analysis set, SAF = safety analysis set.

Diagnosis and criteria for inclusion:

1. Female and male patients with minimal age of 18 years on the date of the first study Visit
2. Stable treatment with OXC (Trileptal® or Timox®), dose: exactly 900 mg, or exactly 1,200 mg, or exactly 1,500 mg, for at least 1 month prior to Screening

3. ≥2 partial onset seizures with or without secondary generalization refractory to existing anti-epileptic drug (AED) therapy within the baseline period
4. Weight between ≥50 kg and <100 kg
5. For females with child-bearing potential: negative pregnancy test and highly effective form of birth control (females using hormonal contraceptives should have used a different or additional means of birth control, e.g. intrauterine device, abstinence, vasectomized partner, double barrier methods with or without oral contraceptives)
6. Stable regimen of ≤2 concomitant AEDs (vagus nerve stimulator included) during the baseline period; lamotrigine dose may be adjusted at Baseline
7. Ethnic origin: Caucasian
8. Patients capable of complying with the study stipulations
9. Patients who provided written informed consent to participate in this study

Test product, dose, mode of administration, batch no.:
OXC modified release 300 mg tablet (OXC MR, Apydan® extent), total daily dose maximum 2,700 mg, oral administration, batch numbers: 0006003512, 0006005848, 0008004093

Reference product, dose, mode of administration, batch no.:
OXC immediate release 300 mg tablet (OXC IR, Trileptal®), total daily dose maximum 2,700 mg, oral administration, batch number: 0006003513, 0006005849, 0008004107

Duration of treatment: 26 days

Criteria for evaluation:

Efficacy

- Primary efficacy variable: final dose with which the patient did not experience any intolerable AEs.
- Secondary efficacy variable: number of seizures during treatment period.

Safety

- Secondary safety variables:
  - Patient performance and cognition at Visit 1, Visit 2, and Final Visit using EpiTrack;
  - AEP Plus questionnaire scores before and after medication intake at each Visit.
- Other safety variables: AEs, vital signs and body weight, electrocardiogram (ECG), laboratory parameters, physical and neurological examinations, concomitant medication, exposure and compliance.

Pharmacokinetic

- Plasma concentrations of OXC and S- and R-MHD. The results will be presented as a supplement to this report.

Statistical methods:

As the study was stopped prematurely with a sample size smaller than planned, all tests were exploratory. The study used an adaptive design according to Bauer and Köhne, based on the primary efficacy variable maximum tolerated dose. The following test decision was used:

Final analysis $p_1 * p_2 > c_\alpha = 0.00870 \Rightarrow$ accept H_0 $p_1 * p_2 \leq c_\alpha = 0.00870 \Rightarrow$ reject H_0

with: p_1 = p-value achieved in the interim analysis, p_2 = p-value achieved from the new data accumulated after the interim analysis, α_0 = upper critical boundary for interim p-value (p1), α_1 = lower critical boundary for interim p-value (p1), c_α = critical value for the product of the p-values from interim and final (p1 * p2).

Due to the adaptive design, separate statistical analyses for patients from the interim analysis and patients from after the interim analysis (primary analysis) and pooled for all patients (secondary analysis) were done for the primary efficacy variable.

A two-sided Wilcoxon test with a significance level of 0.05 was applied for the primary efficacy varibale, the secondary efficacy variable, and the secondary safety variables. Demographic data, AEs, and other safety parameters were summarized descriptively.

SUMMARY - CONCLUSIONS

Patient disposition

A total of 81 patients were screened and 71 patients were randomized: 35 patients in the OXC MR group and 36 patients in the OXC IR group. There were three early terminations, one in the OXC MR group and two in the OXC IR group. Altogether 34 patients in each group completed the study as scheduled.

Demography and baseline characteristics

The treatment groups were balanced based on sex and OXC dose at Baseline. Altogether 53.5% of the study participants were male and 46.5% were female. The Baseline dose was the same in each group for both the ITT and PP populations. Grouped by Baseline OXC dose, 45.1% of patients took 900 mg, 43.7% took 1,200 mg, and 11.3% took 1,500 mg.

Results - Efficacy

Maximum tolerated dose of study drug: The median and mean maximum tolerated doses were higher in the OXC MR group than the OXC IR group for both the interim analysis and after interim analysis populations comprising the primary analysis. The difference was not statistically significant but this was not expected due to the small sample size and power of about 45%. There was a statistically significant difference between the treatment groups based on all patients in the secondary analysis, in favor of the OXC MR group and with a larger difference in the PP population (ITT: $p = 0.0220$; PP: $p = 0.0163$). Patients with a higher baseline dose achieved a higher maintenance dose. More patients had an up-titration

and fewer patients had a down-titration of study drug in the OXC MR group compared to the OXC IR group.

Number of seizures: The number of seizures during the treatment period was similar between the OXC MR and OXC IR treatment groups. There was a median absolute change of -1.8 seizures in the OXC MR group and -2.0 in the OXC IR group comparing the treatment period to the Baseline period.

Results - Secondary safety variables

Epitrack, patient performance and cognition: There was no difference between the treatment groups in the median EpiTrack scores at each Visit. From Visit 1 to the Final Visit, in both treatment groups, the number of patients classed as inconspicuous increased by about 16% and the number of patients classed as impaired decreased by about 13%.

AEP Plus, impairment by seizures: In general, more patients in the OXC MR group than the OXC IR group were not impaired by seizures in their physical and psychic well-being and their work ability and performance. Only a few patients in each group at each study day were very much impaired by seizures.

AEP Plus, AED seizure control, tolerability and impairment by side effects: Seizure control improved in both treatment groups. The percentage of patients rating seizure control as good varied throughout the study, with no large difference between the groups. More patients in the OXC MR group than the OXC IR group rated the tolerability of the AEDs as good. More patients in the OXC MR group had no impairment on physical and psychic well-being and work ability and performance by the side effects of medication.

AEP Plus, psychic state: The percentage of patients with irritability remained the same in both groups throughout the study. There was no general improvement or worsening of depression during the study. The number of patients with anxiety was higher in the OXC IR group than the OXC MR group at each study day, except for Visit 1.

AEP Plus, assessment of 19 side effects: The median sum of the frequency of side effects, the impairment due to side effects, and the relationship of the study medication to the side effects was higher (i.e. the side effects were worse) in the OXC IR group than the OXC MR group.

Results - Other safety variables

A summary of AEs is provided in the table below.

	OXC MR (N = 35)	OXC IR (N = 36)
Number of AEs	127	173
Number (%) of SAEs	1 (0.8)	3 (1.7)
Number (%)[a] of related AEs	104 (81.9)	138 (79.8)
Number (%)[b] of patients with AEs	33 (94.3)	35 (97.2)
Number (%)[b] of patients with SAEs	1 (2.9)	2 (5.6)
Number (%)[b] of patients with definitely related AEs	3 (8.6)	2 (5.6)
Number (%)[b] of patients with probably related AEs	9 (25.7)	17 (47.2)
Number (%)[b] of patients with possibly related AEs	27 (77.1)	27 (75.0)

[a] Percentages are based on the total number of events per treatment group.
[b] Percentages are based on the total number of patients per treatment group.
AE = adverse event, IR = immediate release, MR = modified release, N = number of patients, OXC = oxcarbazepine, SAE = serious adverse event.

Adverse events: Fewer AEs were reported in the OXC MR group (127 AEs in 33 patients) than in the OXC IR group (173 AEs in 35 patients). Nervous system disorders were the most frequent AEs in each group (OXC IR: 89% of patients, OXC MR: 66%), followed by AEs in the class 'general disorders and administration site conditions', affecting about 40% of patients in each group. Approximately 30% of patients in each group had AEs in the system organ classes 'eye disorders' and 'gastrointestinal disorders'. About 80% of all AEs in each treatment group were judged to be related (possibly, probably, or definitely related) to the study medication. The majority of AEs in the OXC MR group were mild (58% of AEs). In the OXC IR group 45% and 50% of AEs were described as mild or moderate, respectively. There was one SAE in the OXC MR group and three SAEs in two patients in the OXC IR group. One patient developed a SUSAR during the compassionate use program. There were no patient deaths.

Clinical laboratory evaluations: No clinically significant abnormalities were reported.

Vital signs, body weight, and ECG: The median values for the vital signs, body weight, and ECG parameters remained the same in each treatment group. There were no clinically significant ECG findings.

Physical and neurological examinations: One patient in the OXC MR group and two patients in the OXC IR group had changes from normal to abnormal findings in the physical examination. No patients had changes in neurological findings from normal to abnormal.

Conclusions:

- The study was prematurely terminated and was therefore not powered to show significant results
- Patients taking OXC MR reached a higher maintenance dose than patients taking OXC IR
- The maintenance dose reached with OXC MR was safe and well tolerated
- More patients in the OXC MR group were not impaired by seizures or AED side effects
- OXC MR appeared to be better tolerated than the IR formulation

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