Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-000079-31	
Name of active ingredient: BI 44370 TA		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 DEC 2009	**Trial No. / U No.:** 1246.04 / U09-2478-01	**Date of trial:** 20 AUG 2008 – 26 MAY 2009	**Date of revision** (if applicable)**:** Not applicable

Title of trial:	A randomised, double-blind, placebo- and active comparator-controlled, five parallel groups study to investigate the efficacy and safety of BI 44370 TA (50 mg, 200 mg, and 400 mg) administered orally once during an acute migraine attack of moderate or severe intensity
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, 47 centres in 8 European countries
Publication (reference):	Data of this study have not been published.
Clinical phase:	II
Objectives:	The objective was to assess the safety, tolerability, and efficacy of 3 doses of BI 44370 TA (50 mg, 200 mg, and 400 mg) for treatment of an acute migraine attack of moderate or severe intensity in comparison with placebo and an active comparator (40 mg eletriptan).
Methodology:	Randomised, placebo- and active comparator-controlled, double-blind, double-dummy, parallel-group design with 5 treatment groups. Each of the 5 treatment groups (50 mg, 200 mg, and 400 mg BI 44370 TA, placebo, and 40 mg eletriptan) consisted of approximately 82 patients. The trial medication was administered once during a fully-developed migraine attack with pain of moderate or severe intensity.

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No. of patients:	
planned:	entered: 410
actual:	enrolled: 470 entered: 416 50 mg BI 44370 TA: entered: 79 treated: 64 analysed (for primary endpoint): 64 200 mg BI 44370 TA: entered: 85 treated: 65 analysed (for primary endpoint): 65 400 mg BI 44370 TA: entered: 84 treated: 73 analysed (for primary endpoint): 73 Placebo: entered: 84 treated: 70 analysed (for primary endpoint): 70 40 mg eletriptan: entered: 84 treated: 69 analysed (for primary endpoint): 69
Diagnosis and main criteria for inclusion:	Patients (aged 18 to 65 years) with migraine, with or without aura, were included in this trial. The migraine had to be diagnosed according to the International Classification of Headache Disorders (2nd edition). Patients had to have an established migraine diagnosis for at least 1 year with the first migraine attack before or at the age of 50 years. The migraine attacks (with pain of moderate or severe intensity) had to persist for at least 6 h and occur 2 to 8 times per month for the 3 months prior to enrolment (up to 12 days with migraine per month were allowed). Other forms of headache were permitted if they occurred on average up to 10 days per month and if the patient was able to distinguish migraine headache from other forms of headache. Patients had to be in general good health based on the screening assessment.
Test product:	BI 44370 TA tablet
dose:	50 mg, 200 mg, or 400 mg (2 tablets of 200 mg) single dose
mode of admin.:	oral
batch no.:	B081001464 (50 mg) and B081001456 (200 mg)

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Reference therapy 1:	Placebo tablet (matching BI 44370 TA tablet)	
dose:	Not applicable	
mode of admin.:	Oral	
batch no.:	B081002004 (50 mg placebo), B081001896 (200 mg placebo)	
Reference therapy 2:	Eletriptan capsule	placebo capsule (matching eletriptan capsule)
dose:	40 mg single dose	not applicable
mode of admin.:	Oral	oral
batch no.:	B081001050 (40 mg eletriptan)	B081001021 (40 mg placebo)
Duration of treatment:	single dose	

Criteria for evaluation:

Efficacy:

The primary endpoint was pain-free response 2 h after study drug intake, defined as a reduction of a severe or moderate headache to no headache.

Secondary endpoints:

- Pain-free response 0.5, 1, 1.5, 24 and 48 h after study drug intake without intake of rescue medication
- Pain relief (defined as reduction of a severe or moderate headache to mild or no headache) 0.5, 1, 1.5, 2, 24 and 48 h after study drug intake without intake of rescue medication
- Sustained pain-free response (no headache 2 h after study drug intake and remaining pain-free up to 24 and 48 h after study drug intake without intake of rescue medication)
- Sustained pain relief (reduction to mild or no headache 2 h after study drug intake and no worsening up to 24 and 48 h after study drug intake without intake of rescue medication)
- Intensity of headache at the time of study drug intake and 0.5, 1, 1.5, 2, 24 and 48 h after study drug intake
- Relief of migraine-associated symptoms (nausea, vomiting, photophobia, phonophobia) 0.5, 1, 1.5, 2, 24 and 48 h after study drug intake
- Time to meaningful relief (defined subjectively by the patient) in a time frame of 2 h after study drug intake when relief of pain and migraine-associated

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	symptoms became meaningful - Global evaluation of the medication by the patient 48 h after study drug intake - Functional disability (assessed by the patient using a 4-point scale) at the time of study drug intake and 0.5, 1, 1.5, 2, 24 and 48 h after study drug intake - Use of and time to use of rescue medication within 48 h after study drug intake - Recurrence (occurrence of a moderate or severe headache) within 24 and 48 h after study drug intake provided the patient had pain relief 2 h after study drug intake - Relapse (occurrence of a headache of any severity) within 24 and 48 h after study drug intake provided the patient was pain-free 2 h after study drug intake
Safety:	Incidence of adverse events (AE), physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests (haematology, serum chemistry, and urinalysis).
Statistical methods:	Pairwise comparisons were tabulated using Fisher's exact test. Furthermore, the proportion of pain-free patients and those with pain relief 2 h after study drug intake was analysed using an exact conditional test for stratified 2x2 contingency tables considered as a (pooled) coutry-adjusted version of Fisher's exact test. Analysis of safety was done descriptively.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	Of the 416 randomised patients, 341 patients (82.0%) were treated with study medication. The patient population consisted mostly of white patients (87.1%) and the proportion of female patients was 83.3%. The patients had a mean age of 40.2 years. The treatment groups were generally well matched for demographic and baseline parameters. The primary endpoint was pain-free response 2 h after study drug administration. Tests for the primary endpoint analysis followed a pre-specified hierarchical testing procedure. Proof of concept for BI 44370 TA was shown by comparing BI 44370 TA with placebo in a hierarchical testing procedure. Firstly, superiority of the 400 mg BI 44370 TA dose group over placebo was demonstrated. Patients receiving 400 mg BI 44370 TA experienced a significantly larger pain-free response (27.4%, p = 0.0016) when compared with placebo (8.6% with pain-free response). In the subsequent steps, it was shown that neither the 200 mg nor the 50 mg dose of BI 44370 TA reached statistical significance versus placebo,

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	although 21.5% of patients in the 200 mg dose group experienced pain-free response ($p = 0.0346$). The pain-free response rate for the 50 mg BI 44370 TA group (7.8%) was in the range of placebo. As expected, treatment with 40 mg eletriptan (34.8% with pain-free response, $p = 0.0001$) was significantly more efficacious than placebo. The analyses of the secondary endpoints supported the conclusion from the primary analysis. The pain-free response and pain-relief rates obtained at various time points (from 30 min to 48 h after dosing) showed better efficacy of the 400 mg and 200 mg doses of BI 44370 TA and the 40 mg eletriptan dose in comparison with placebo. At the 24 h and 48 h time points, patients receiving 400 mg and 200 mg doses of BI 44370 TA as well as patients treated with 40 mg eletriptan had significantly larger pain-free response rates than patients treated with placebo ($p < 0.025$). Patients treated with 400 mg BI 44370 TA achieved significant sustained pain-free response rates both 24 h and 48 h after dosing ($p < 0.025$) when compared to placebo. In contrast, patients treated with 40 mg eletriptan achieved statistical significance (versus placebo) for sustained pain-free response only 24 h after dosing. The analysis of (sustained) pain relief was generally consistent with the results of (sustained) pain-free response. The results of all other endpoints (intensity of headache, relief of migraine-associated symptoms, time to meaningful relief, time to use of RM, functional disability of the patients, recurrence/relapse of headache, and global evaluation of the study medication) supported the results of the primary endpoint. Finally, efficacy of BI 44370 TA was shown although the majority of patients had eaten a light snack or a full meal within 6 h before study drug intake.
Safety results:	In this trial, a total of 341 patients were treated with study medication and received a single dose of either placebo, 50 mg BI 44370 TA, 200 mg BI 44370 TA, 400 mg BI 44370 TA, or 40 mg eletriptan. During the treatment period, 23 patients (11.4%) in the BI 44370 TA groups, 7 patients (10.0%) in the placebo group, and 12 patients (17.4%) in the 40 mg eletriptan group experienced at least one AE. The incidence of AEs was lowest in the 200 mg BI 44370 TA group and highest in the 50 mg BI 44370 TA group.

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No dose dependent increase of AE frequency was observed for treatment with BI 44370 TA.

The most frequently reported AEs by system organ class (incidence ≥5%) were nervous system disorders, gastrointestinal disorders, and general disorders and administration site conditions. Nervous system disorders were reported by 3.0% of patients in the BI 44370 TA groups, by 5.7% of patients in the placebo group, and by 7.2% of patients in the 40 mg eletriptan group. The highest incidence of nervous system disorders among the BI 44370 TA groups was in the 50 mg dose group (6.3%); however, nervous system disorders did not occur in the 400 mg dose group. Within nervous system disorders, the AEs with the highest incidence by preferred term were allodynia, dizziness, tension headache and tremor (overall incidence of 0.6%).

AEs of severe intensity during the treatment period were reported by only 1 patient (0.5%) in the BI 44370 TA groups (diarrhoea in the 400 mg group) and 3 patients (4.3%) in the 40 mg eletriptan group (diarrhoea, fatigue, and sciatica). During the post-treatment period, 3 patients (randomised to 200 mg BI 44370 TA and 40 mg eletriptan) experienced severe AEs (sciatica, migraine, and vomiting). Drug-related were recorded for 9 patients (4.5%) in the BI 44370 TA groups, for 1 patient (1.4%) in the placebo group and for 6 patients (8.7%) in the 40 mg eletriptan group. The incidence of drug-related AEs did not correlate with increasing doses of BI 44370 TA.

No clinically significant treatment differences were observed in either the mean changes in laboratory values from baseline to last value on treatment or in the frequency of patients with transitions relative to reference range in the majority of the patients. PCSAs were most frequently reported for manual cell count (eosinophils) in the 50 mg BI 44370 TA group. The detected PCSAs were considered as not clinically relevant. During the post-treatment period, 6 patients showed changes in laboratory parameters which were reported as AEs: 3 patients (treated with placebo and 200 mg BI 44370 TA) had increased blood creatinine phosphokinase values, 2 patients (randomised to placebo and 400 mg BI 44370 TA) had abnormal liver function tests, and 1 patient (treated with 50 mg BI 44370 TA) had increased blood bilirubin levels. No dose dependency in the incidence of AEs was observed. For ECG results, mean pulse rate and blood pressure, no relevant changes were noted during the trial.

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Conclusions:

Proof of concept was shown for treatment with BI 44370 TA in migraine patients. The analysis of the primary endpoint showed increasing pain-free response rates for increasing doses of BI 44370 TA: the 400 mg BI 44370 TA dose was about as efficacious as the 40 mg eletriptan dose (both statistically significant in comparison with placebo), the 200 mg BI 44370 TA dose showed a numerically higher response rate than placebo, and finally the 50 mg BI 44370 TA dose was in the range of placebo. The analyses of the secondary endpoints supported the conclusion from the primary analysis. Efficacy of BI 44370 TA was shown although the majority of patients had eaten a light snack or a full meal within 6 h before study drug intake.

Treatment with BI 44370 TA was well tolerated. The incidence of AEs was low and did not correlate with increasing doses of BI 44370 TA. Overall, no relevant drug-related safety issues were identified.