Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-019052-45	
Name of active ingredient: Ibuprofen and pseudoephedrine HCl		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 21 FEB 2011	**Trial No. / U No.:** 1024.7 / U11-1140-01	**Dates of trial:** 27 JUL 2010 – 15 SEP 2010	**Date of revision:** Not applicable

Title of trial:	Bioequivalence of a fixed-dose combination tablet containing 200 mg ibuprofen and 30 mg pseudoephedrine HCl compared to RhinAdvil® (200 mg ibuprofen and 30 mg pseudoephedrine HCl) as a fixed-dose combination tablet administered in healthy male and female volunteers (open-label, randomised, single dose, two-way crossover, Phase I trial)
Principal Investigator:	[redacted]
Trial site:	Department of Translational Medicine, Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG Ingelheim am Rhein Germany
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	To assess whether the fixed-dose combination (FDC) of ibuprofen and pseudoephedrine HCl tablet manufactured by Boehringer Ingelheim is bioequivalent to the commercial product RhinAdvil®
Methodology:	Randomised, controlled, open-label, 2-way crossover design; single dose trial
No. of subjects:	
planned:	Entered: 48
actual:	Entered: 47 Test treatment: 200 mg ibuprofen and 30 mg pseudoephedrine HCl (BI-FDC): entered: 47, treated: 47, analysed (for primary endpoint): 45 Reference treatment: 200 mg ibuprofen and 30 mg pseudoephedrine HCl (RhinAdvil®): entered: 46, treated: 46, analysed (for primary endpoint): 45
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥21 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2. At least 16 subjects of each sex were to be randomised.

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Test product:	Ibuprofen and pseudoephedrine HCl film-coated tablet (BI-FDC)
dose:	200 mg ibuprofen and 30 mg pseudoephedrine HCl
mode of admin.:	Oral administration with 240 mL water, after an overnight fast of at least 10 h
batch no.:	B101002310/SP010310
Reference therapy:	Ibuprofen and pseudoephedrine HCl tablet (RhinAdvil®)
dose:	200 mg ibuprofen and 30 mg pseudoephedrine HCl
mode of admin.:	Oral administration with 240 mL water, after an overnight fast of at least 10 h
batch no.:	B101002304/9EN058
Duration of treatment:	Single dose of test and reference treatment, in each case followed by 30 h of pharmacokinetic sampling. A wash-out phase of at least 5 days separated drug administration in the first and second treatment periods.
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints: AUC_{0-tz} and C_{max} of ibuprofen and pseudoephedrine HCl Secondary endpoints: $AUC_{0-\infty, obs}$, $AUC_{0-\infty, pred}$, t_{max}, AUC_{t1-t2}, λ_z, $t_{1/2}$, MRT_{po}, $\%AUC_{tz-\infty}$, CL/F, V_z/F of ibuprofen and pseudoephedrine HCl
Safety:	Physical examination, assessment of blood pressure and pulse rate, 12-lead ECG, safety laboratory tests, recording of adverse events (AEs), and assessment of global tolerability
Statistical methods:	The geometric mean (gMean) point estimators for the median intra-subject ratios of C_{max} (test treatment) to C_{max} (reference treatment) and for AUC (test treatment) to AUC (reference treatment) were calculated. An analysis of variance (ANOVA) was performed on log-transformed parameters, and included effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. Based on the residual error from the ANOVA model, 2-sided 90% confidence intervals (CIs) for the intra-subject ratios were calculated in order to determine whether the CIs fell in the pre-defined range of 80 to 125% of the reference treatment. For all other parameters, descriptive statistics were calculated.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

A total of 47 subjects was entered in the trial. All subjects received at least 1 dose of trial medication. Data from 45 subjects were included in the PK analysis set for assessment of of primary endpoints (1 subject did not attend the second trial period for personal reasons, and 1 subject was excluded due to use of a prohibited concomitant therapy). Of the 47 subjects included in the trial, 24 (51.1%) were male and 23 (48.9%) were female. All subjects were of white race. Mean age was 33.8 years, and mean BMI was 24.8 kg/m^2. No subject reported a concomitant medical diagnosis; 4 subjects (8.5%) reported intake of concomitant medication.

Ibuprofen

Evaluation of ibuprofen plasma concentration-time profiles indicated similar absorption for BI-FDC and RhinAdvil®, but with a median t_{max} for BI-FDC occuring approximately 0.5 h later than for RhinAdvil®. Exponential decay characteristics were similar between the formulations. Assessment of PK parameters for ibuprofen indicated similar characteristics of the formulations: gMean values for C_{max} were alike, with low interindividual variation. Ranges of t_{max} values overlapped almost entirely for the 2 formulations (0.750 to 3.98 h for BI-FDC, and 0.500 to 3.97 h for RhinAdvil®). Geometric mean values of AUC_{0-tz} were also substantially the same between the formulations, also with low interindividual variation. Terminal half-life, mean residence time of the analyte, oral clearance, and apparent volume of distribution were similar between the 2 formulations.

An inferential statistical analysis was performed using the PK analysis set in order to assess bioequivalence of ibuprofen for primary PK parameters (AUC_{0-tz} and C_{max}; see table below).

Ibuprofen	Adjusted gMean BI-FDC (test) (N=45)	Adjusted gMean RhinAdvil® (reference) (N=45)	Adjusted gMean ratio Test/reference [%]	Intra-indiv. gCV [%]	2-sided 90% CI Lower limit [%]	2-sided 90% CI Upper limit [%]
AUC_{0-tz} [µg·h/mL]	58.6	57.7	101.6	7.9	98.8	104.5
C_{max} [µg/mL]	14.8	16.0	92.3	18.1	86.5	98.3

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Clinical pharmacology results (continued):

Key secondary PK parameters ($AUC_{0-\infty,pred}$, $AUC_{0-\infty,obs}$) were similarly assessed. Using the PK analysis set, the point estimates for relative exposure for all primary and secondary parameters were between 92.3% and 101.8%, with 90% CI values between 86.5% and 104.6%. Therefore, the 90% CIs were in the range from 80 to 125% that was pre-defined as establishing bioequivalence between BI-FDC and RhinAdvil®.

Pseudoephedrine

Evaluation of pseudoephedrine plasma concentration-time profiles demonstrated essentially overlying profiles for BI-FDC and RhinAdvil® for both absorption and exponential decay phases. Pharmacokinetic characteristics of the 2 formulations were similar. Geometric mean values for C_{max} and AUC_{0-tz} were alike, with low interindividual variation. Median t_{max} values were also similar (data ranges 0.483 to 2.98 h for BI-FDC, and 0.500 to 2.98 h for RhinAdvil®). Terminal half-life, mean residence time of the analyte, oral clearance, and apparent volume of distribution were similar between the 2 formulations.

An inferential statistical analysis was performed using the PK analysis set in order to assess bioequivalence of pseudoephedrine for primary PK parameters (AUC_{0-tz} and C_{max}; see table below).

Pseudo-ephedrine	Adjusted gMean BI-FDC (test) (N=45)	Adjusted gMean RhinAdvil® (reference) (N=45)	Adjusted gMean ratio Test/reference [%]	Intra-indiv. gCV [%]	2-sided 90% CI Lower limit [%]	2-sided 90% CI Upper limit [%]
AUC_{0-tz} [µg·h/mL]	1.08	1.09	99.7	11.6	95.6	103.8
C_{max} [µg/mL]	0.143	0.139	102.9	18.4	96.5	109.8

Key secondary PK parameters ($AUC_{0-\infty,pred}$, $AUC_{0-\infty,obs}$) were similarly assessed. Using the PK analysis set, the point estimate for relative exposure for all primary and secondary parameters was between 99.7% and 102.9%, with 90% CI values between 95.6% and 109.8%. Therefore, the 90% CIs were in the range from 80 to 125% that was pre-defined as establishing bioequivalence between BI-FDC and RhinAdvil®.

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Safety results:

Of the 47 subjects, 47 (100%) were administered BI-FDC, and 46 (97.9%) were administered RhinAdvil® (1 subject did not return for the trial period in which RhinAdvil® was administered). All subjects to whom treatment was administered were included in the analysis of safety.

During the trial as a whole, of 47 subjects, 8 (17.0%) reported AEs. No AEs were reported for the screening or post-study periods. There were no deaths, other serious AEs, or other significant AEs (ICH E3 definition) reported. All AEs reported during the trial resolved by the end of the trial.

During the study period in which RhinAdvil® was administered, 6 subjects (13.0%) reported AEs: 3 subjects reported mild headache, 1 subject reported severe headache, 1 subject reported severe headache and severe vomiting, and 1 subject reported severe influenza. The investigator considered the vomiting and all cases of headache as related to trial medication, for a total number of 5 subjects (10.9%) with drug-related AEs.

During the study period in which BI-FDC was administered, 3 subjects (6.4%) reported AEs: 1 subject reported mild headache, 1 subject reported moderate phlebitis, and 1 subject reported mild nasopharyngitis. The investigator considered the headache as related to trial medication, for a total of 1 subject (2.1%) with drug-related AEs.

For individual subjects, occasional safety laboratory values were identified that were above or below the reference ranges; however, none of these were assessed as clinically significant by the investigator. There were no vital signs assessments or ECG measurements reported as clinically significant by the investigator. The investigator assessed the tolerability of treatment as 'good' for all subjects participating in each study period.

Conclusions:

Bioequivalence was established for ibuprofen and pseudoephedrine administered as BI-FDC compared with ibuprofen and pseudoephedrine administered as RhinAdvil®. There were no findings in the trial that indicated safety concerns for administration of BI-FDC to healthy adults.