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: Buscopan®		**EudraCT No.:** 2012-003720-20	
Name of active ingredient: Hyoscine butylbromide (AD 1 Br)		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 AUG 2013	**Trial No. / U No.:** 202.846 / U13-2064-01	**Dates of trial:** 27 NOV 2012–27 DEC 2012	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability study to investigate and to compare two different formulations of hyoscine butylbromide, following oral administration in healthy male and female volunteers (an open-label, randomised, single-dose, two-way crossover, Phase I study)
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Str. 173, Ingelheim/Rhein, Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of hyoscine butylbromide drops (test formulation, 10 mg/mL) compared with Buscopan® sugar-coated tablets (reference formulation, 10 mg) following oral administration of a single dose of 20 mg in healthy male and female volunteers.
Methodology:	An open-label, randomised, single-dose, two-way crossover study with a wash-out period of at least 7 days. Each subject was to receive both treatments.
No. of subjects:	
planned:	Entered: 30 subjects
actual:	Test (T) treatment: hyoscine butylbromide drops: treated: 30 analysed (for primary and secondary endpoints): 27 Reference (R) treatment Buscopan® sugar-coated tablets: treated: 28 analysed (for primary and secondary endpoints): 27
Diagnosis and main criteria for inclusion:	Healthy volunteers, male and female, age ≥18 to ≤50 years, body mass index (BMI) ≥18.5 to ≤29.9 kg/m^2
Test product:	Hyoscine butylbromide as drops (10 mg/mL)
dose:	20 mg

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mode of admin.:	Oral administration of 2 mL with 240 mL water after an overnight fast
batch no.:	B121003336
Reference therapy:	Buscopan®: hyoscine butylbromide as sugar-coated tablets (10 mg)
dose:	20 mg
mode of admin.:	Oral administration of 2 tablets with 240 mL water after an overnight fast
batch no.:	B121003179
Duration of treatment:	The subjects were to undergo 2 treatment periods and were to receive a single dose of trial medication (R or T) in each treatment period. The 2 drug administrations were separated by a washout phase of at least 7 days.
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic (PK) parameters of hyoscine butylbromide: Primary endpoints: AUC_{0-tz} and C_{max} Secondary endpoint: $AUC_{0-\infty}$
Safety:	Evaluation of adverse events, vital signs (blood pressure, pulse rate, occurrence of findings), physical examination (occurrence of findings), 12-lead ECG, safety laboratory parameters
Statistical methods:	Pharmacokinetic parameters were summarised using descriptive statistics. The assessment of relative bioavailability was based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (T/R). The statistical model used was ANOVA on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. Safety and tolerability were assessed using descriptive statistics.

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SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

Of the 30 treated subjects, 16 (53.3%) were female and 14 (46.7%) were male. All subjects were of White race. Median age (range) was 37.5 years (23 years, 50 years); median BMI (range) was 25.0 kg/m^2 (19.7 kg/m^2, 29.6 kg/m^2). Primary, secondary, and other PK parameters were initially calculated on the treated set (TS) excluding the drop outs (Subject [redacted]). During statistical analysis, Subject [redacted] was excluded from the PKS following the guideline on the investigation of bioequivalence because the pre-dose plasma concentration of hyoscine butylbromide in period 2 was above 5% of C_{max} for this patient. Thus, the PK analysis data set (PKS) used for inferential statistical analysis of primary and secondary PK endpoints included 27 subjects from the TS.

The plasma concentration-time profiles indicate, that peak concentrations were reached within the first 3 to 4 h for both treatments (t_{max}>3 h). Initially hyoscine butylbromide was more slowly absorbed from the tablet compared with the drops. However over time, the hyoscine butylbromide plasma concentration was slightly higher for the tablet formulation than for the drops. This resulted in a lower C_{max} and AUC_{0-tz} for the drops compared with the tablets. Statistical assessment of the PK-parameters resulted in adjusted gMean ratios T/R of 86.97% for C_{max} and 89.05% for AUC_{0-tz} and indicated that the exposure to hyoscine butylbromide drops was smaller compared with tablets.

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Pharmacokinetic results (continued):

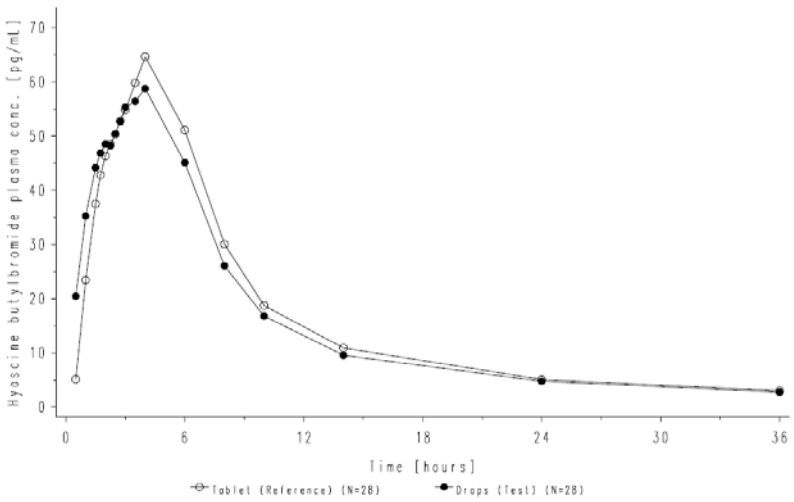

Figure 2.1 Geometric mean plasma concentration-time profiles of hyoscine butylbromide on the linear scale – TS (N = 28)

Table 2.1 Primary PK endpoints – PKS (N = 27)

		T: drops N = 27	R: tablet N= 27
C_{max}	gMean [pg/mL]	68.93	79.26
	Intraindividual gCV [%]	35.6	
	Adjusted gMean ratio T/R [%]	86.97	
AUC_{0-tz}	gMean [pg·h/mL]	557.17	625.71
	Intraindividual gCV [%]	31.2	
	Adjusted gMean ratio T/R [%]	89.05	
$AUC_{0-\infty}$	gMean [pg·h/mL]	614.87	682.99
	Intraindividual gCV [%]	29.3	
	Adjusted gMean ratio T/R [%]	90.03	

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Safety results:	All 30 treated subjects were included in the safety analysis. Of the 30 subjects, 28 received a total dose of 40 mg hyoscine butylbromide within 2 treatment periods (20 mg as drops and 20 mg as tablets). Two subjects (Subject [redacted]) received 20 mg drops only and did not take tablets within the second treatment period. The treatment sequence T-R was completed by 14 subjects (although 16 subjects were planned originally), and the sequence R-T was also completed by 14 subjects. There were no SAEs, or other significant AEs (ICH E3 criteria) reported for administration of hyoscine butylbromide as drops or as tablet. The most frequently reported AEs on the SOC level were nervous system disorders, gastrointestinal disorders, and infections and infestations, each reported with a frequency of 10.0%. All on-treatment AEs were of mild or moderate intensity, and all had resolved by the end of the trial. The investigator considered headache (reported by 2 subjects) and nausea (1 subject) to be drug related. During clinical laboratory evaluation, Subject [redacted] was reported with elevated values for liver enzymes and was withdrawn prior to the second treatment period. It was assumed, that the elevated values resulted from alcohol consumption during the trial, although that was not foreseen (non-drinker, no signs in the acute alcohol breath tests reported). There were no clinically relevant changes in laboratory parameters or in vital signs.
Conclusions:	Hyoscine butylbromide was administered as drops (test treatment) and tablets (reference treatment buscopan). Buscopan is known to have a low bioavailability. In this trial complete plasma concentrations–time profiles were measured for all subjects. The applied analytical method was very sensitive. Statistical assessment of the PK parameters resulted in adjusted gMean ratios T/R of 86.97% for C_{max} and 89.05% for AUC_{0-tz}. Intraindividual variability was above 30% for both, C_{max} and AUC_{0-tz}. Thus, in this initial relative bioavailability study, hyoscine butylbromide drops and tablets show similar plasma concentration-time profiles but differ slightly on a quantitative level. Administration of hyoscine butylbromide drops or tablets to healthy adult volunteers was safe and well tolerated.