



Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		Tabulated Trial Report		 Boehringer Ingelheim Synopsis No.:
Name of finished product: Bisolvon®		EudraCT No.: 2011-002733-19		
Name of active ingredient: Bromhexine hydrochloride		Page: 1 of 5		
Module:		Volume:		
Report date: 09 MAY 2012	Trial No. / U No.: 65.129 / U12-1405-01	Dates of trial: 26 AUG 2011 – 15 OCT 2011	Date of revision: Not applicable	
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Title of trial:	Relative bioavailability of bromhexine for oral administration of 16 mg of bromhexine hydrochloride granules compared to 16 mg of bromhexine hydrochloride syrup in healthy male and female volunteers (an open-label, randomised, single-dose, replicate design Phase I study with two treatments in four crossover periods)			
Principal Investigator:	[REDACTED]			
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG Dept. of Translational Medicine/Human Pharmacology Centre Birkendorfer Straße 65 Biberach/Riss Germany			
Publication (reference):	Data of this trial have not been published			
Clinical phase:	I			
Objectives:	To investigate the relative bioavailability of single doses of 16 mg bromhexine hydrochloride granules (test formulation T) compared with single doses of 16 mg bromhexine syrup (reference formulation R) in healthy volunteers			
Methodology:	Randomised, open-label, single-dose, replicate design study with 2 treatments in 4 crossover periods. A single dose of test or reference treatment was administered in each trial period, and a washout period of at least 7 days separated each administration of trial medication. Pharmacokinetic (PK) sampling points: predose, 20 min, 40 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, and 48 h			
No. of subjects:	<p>planned: entered: 39</p> <p>actual: entered: 39</p> <p>Test treatment (bromhexine granules): entered: 39 treated: 39 analysed (for primary endpoint): 39</p> <p>Reference treatment (bromhexine syrup): entered: 39 treated: 39 analysed (for primary endpoint): 39</p>			

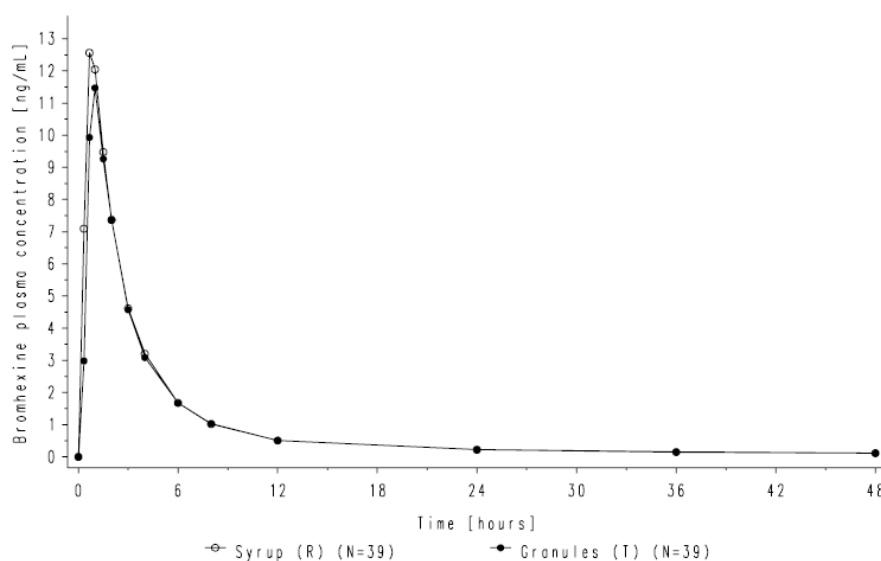
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Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, aged 18 to 55 years, with body mass index (BMI) from 18.5 to 29.9 kg/m ²			
Test product:	Bromhexine hydrochloride granules			
dose:	16 mg (1 single dose in 2 trial periods)			
mode of admin.:	Oral administration without water after an overnight fast			
batch no.:	B111002931			
Reference therapy:	Bromhexine hydrochloride syrup			
dose:	16 mg (1 single dose in 2 trial periods)			
mode of admin.:	Oral administration without water after an overnight fast			
batch no.:	B111000687			
Duration of treatment:	Single dose of either test or reference product in each of 4 trial periods (total of 4 single doses)			
Criteria for evaluation:	<p>Pharmacokinetics: Primary endpoints: AUC_{0-tz} and C_{max} Secondary endpoint: AUC_{0-∞} Other parameters of interest: t_{max}, λ_z, t_{1/2}, %AUC_{tz-∞}, MRT_{po}, CL/F, and V_z/F</p> <p>Safety: Safety was evaluated by physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, laboratory tests, adverse events (AEs), and assessment of global tolerability.</p>			
Statistical methods:	The statistical model for the analysis of relative bioavailability for bromhexine test treatment compared with reference treatment was an analysis of variance (ANOVA) on the logarithmic scale, adapted for replicate design, with 'sequence', 'period', and 'treatment' as fixed effects, and 'subject' as a random effect. For primary and secondary endpoints, the geometric mean (gMean) ratios were calculated. Based on the residual error from ANOVA, 2-sided 90% CIs were also calculated for these endpoints.			


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SUMMARY – CONCLUSIONS:

Pharmacokinetic results: In total, 39 healthy subjects were entered and administered trial medication. All subjects received all doses of trial medication and completed the planned observation time. Of the 39 subjects, 38 were of white race, 1 was of black race, and the mean age was 34.7 years (range 20 to 54 years). Data from all 39 subjects were included in the PK analysis.

Geometric mean plasma time-concentration profiles were quite similar for the syrup and the granule formulations. Exposure to bromhexine was comparable for the test treatment compared with the reference treatment: adjusted gMean AUC_{0-tz} was 45.4 ng·h/mL for the test treatment and 48.4 ng·h/mL for the reference treatment; adjusted gMean $AUC_{0-\infty}$ was 48.8 ng·h/mL for the test treatment and 51.5 ng·h/mL for the reference treatment; and adjusted gMean C_{max} was 14.3 ng/mL for the test treatment and 16.9 ng/mL for the reference treatment. The time to maximum plasma concentration was similar between the formulations, and the elimination phase was identical (see figure below).



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Pharmacokinetic results (cont.):

Statistical assessment of AUC_{0-tz} and AUC_{0-∞} also indicated that exposure to bromhexine from the test formulation was similar to the reference formulation: gMean ratios were 93.85% for AUC_{0-tz} and 94.74% for AUC_{0-∞}; the 90% CIs were within the standard bioequivalence acceptance range of 80.00 to 125.00%. For C_{max} the gMean ratio was 84.37% and the lower end of the 90% CI was 77.73%, 2.27% below the lower end of the standard confidence interval.

	Test ^b		Reference ^b		Test/ref adj gMean ratio (%)	90% CI (%)
	Adj. gMean	gCV ^a (%)	Adj. gMean	gCV ^a (%)		
AUC _{0-tz} (ng·h/mL)	45.43	14.03	48.41	15.69	93.85	90.20 to 97.64
AUC _{0-∞} (ng·h/mL)	48.83	13.73	51.54	15.52	94.74	91.11 to 98.51
C _{max} (ng/mL)	14.27	32.30	16.91	29.98	84.37	77.73 to 91.57


^aintraindividual
^bN=39 for both test and reference treatments

Safety results:

All 39 subjects received all 4 planned doses of bromhexine (total dose of 64 mg per subject).

Of the 39 treated subjects, 8 (20.5%) reported 1 or more AEs in any treatment period. Including all treatment periods, the system organ class categories reported by the largest number of subjects were nervous system disorders, musculoskeletal and connective tissue disorders, and reproductive system and breast disorders, each in 2 of 39 subjects (5.1%). No preferred term was reported for more than 1 subject. No subject discontinued trial participation due to any AE. The investigator did not report that any AE was related to treatment with trial medication. There were no AEs of severe intensity reported for any subject. No deaths, serious AEs, or other significant AEs were reported.

No clinical laboratory assessment for any subject was considered to be of clinical relevance by the investigator or was reported as an AE. There were no clinically relevant changes in systolic or diastolic blood pressures or pulse rate for any subject. Global tolerability of treatment was rated by the investigator as 'good' for all subjects in all trial periods.

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Conclusions: The single dose replicate design trial of bromhexine granules (test) compared with bromhexine syrup (reference) demonstrated that for the parameters AUC _{0-tz} and AUC _{0-∞} the adjusted gMean ratio (point estimate) and 90% confidence interval were well within the limits of the standard bioequivalence acceptance criteria of 80.00 to 125.00%. Therefore, comparable total exposure was achieved for the granulate compared with the syrup. For the granulate, the lower end of the 90% confidence interval for C _{max} was 2.3% below the lower bioequivalence limit of 80.00%. Nevertheless, the overall maximal exposure for the 2 formulations can be regarded as similar. Considering that efficacy of bromhexine is likely to be determined primarily by total exposure of the compound and less substantially by peak exposure, the observed trend towards slightly lower C _{max} values for the granulate should not be of clinical relevance. Safety and tolerability were very good for both formulations.				