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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Lasolvan®		**EudraCT No.:** Not applicable	
BI Investigational Products: Lasolvan® (ambroxol) prolonged-release hard capsules 75 mg Lasolvan® (ambroxol) effervescent tablets 60 mg		**Page:** 1 of 9	
Report Date: 27 NOV 2014	**Trial No. / Doc. No.:** 18.510 / c02558325-02	**Dates of Trial:** 07 March 2014 – 19 May 2014	**Date of Revision:** 11 MAR 2015

Title of Trial:	An open-label, randomized, multiple-dose, three-period crossover study in healthy male and female volunteers to characterize pharmacokinetics and assess the relative bioavailability of two new oral formulations of ambroxol hydrochloride as Lasolvan® prolonged-release hard capsules 75 mg and Lasolvan® effervescent tablets 60 mg compared to Lasolvan® tablets 30 mg.
Principal/Coordinating Investigator:	[redacted]
Trial Site:	[redacted]
Publications:	Data from this trial have not been published at the time of this report.
Clinical Phase:	I
Objectives:	*Primary objectives:* 1. To study the total and peak exposure of ambroxol hydrochloride from two new oral formulations, Lasolvan® prolonged-release hard capsules 75 mg and Lasolvan® effervescent tablets 60 mg, and from reference formulation, Lasolvan® tablets 30 mg. 2. To assess the relative bioavailability of Lasolvan® prolonged-release hard capsules 75 mg with respect to Lasolvan® tablets 30 mg. 3. To assess the relative bioavailability of Lasolvan® effervescent tablets 60 mg with respect to Lasolvan® tablets 30 mg. *Secondary objectives:* 1. To test equivalence of total exposure after dose adjustment between Lasolvan® prolonged-release hard capsules 75 mg and Lasolvan® tablets 30 mg.

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	2. To test equivalence of total exposure after dose adjustment between Lasolvan® effervescent tablets 60 mg and Lasolvan® tablets 30 mg. 3. To test equivalence of total exposure after dose adjustment between Lasolvan® prolonged-release hard capsules 75 mg and Lasolvan® effervescent tablets 60 mg. 4. To study the safety and tolerability of multiple-dosing of Lasolvan® prolonged release hard capsules 75 mg and Lasolvan® effervescent tablets 60 mg compared to Lasolvan® tablets 30 mg.
Methodology:	This was an open-label, randomized, balanced, multiple-dose, three-period, three treatment, six-sequence crossover study. The study was conducted in healthy male and female volunteers, in one clinical trial center within the Russian Federation.
No. of Subjects:	
Planned:	Entered: 24
Actual:	Enrolled: 29
	Entered: 24
	Lasolvan® prolonged-release hard capsules 75 mg (T1)
	Entered: 24 Treated: 24 Analysed (for primary endpoint): 23
	Lasolvan® effervescent tablets 60 mg (T2)
	Entered: 24 Treated: 24 Analysed (for primary endpoint): 23
	Lasolvan® tablets 30 mg (R)
	Entered: 24 Treated: 23 Analysed (for primary endpoint): 23
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male and female subjects, given written informed consent, age 18 to 45 years, body mass index (BMI) 18.50 to 24.99 kg/m^2
BI Investigational	Lasolvan® prolonged-release hard capsules 75 mg

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Product #1:	
Dose:	One capsule (1 x 75 mg) once daily for 5 days.
Mode of Admin.:	Oral
Batch No.:	B131001200
BI Investigational Product #2	Lasolvan® effervescent tablets 60 mg
Dose:	One-half effervescent tablet (½ x 60 mg) twice daily with a 12-h interval between doses for 5 days
Mode of Admin.:	Oral
Batch No.:	B131001200
Comparator Product:	Lasolvan® tablet 30 mg
Dose:	One tablet (1x30 mg) twice daily with a 12-h interval between doses for 5 days
Mode of Admin.:	Oral
Batch No.:	244806
Duration of Treatment:	Three 6-day treatment periods separated by 6-day washout periods (active treatment was administered during first 5 days of each treatment period).
Criteria for Evaluation:	Primary endpoints: $AUC_{ss\ 0\text{-}24}$, $C_{max\ ss}$,
Efficacy / Clinical Pharmacology / Other:	Secondary endpoints: $AUC_{ss\ 0\text{-}24\ norm}$, $C_{max\ ss}/AUC_{ss0\text{-}24}$, $C_{min\ ss}$, $C_{av\ ss}$, $t_{max\ ss}$, PTF, PTS, T ($C>C_{av\ ss}$), T ($C>75\%C_{max\ ss}$).
Safety:	Physical examination, global assessment, vital signs (blood pressure, pulse rate, body temperature), laboratory tests, 12-lead ECG, adverse events.
Statistical Methods:	*Regarding primary endpoints:* The assessment of bioequivalence without molar mass adjustment (dose adjustment) was based upon two-sided 90% confidence intervals (CIs) for the

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ratios of the geometric means (test/reference) of the peak concentration ($C_{max\ ss}$) using an acceptance range of 75%-133%, whereas for the ratios of the geometric means (test/reference) of the total exposure ($AUC_{ss\ 0-24}$) the acceptance range of 80%-125% was used.

Regarding secondary endpoints:

The assessment of bioequivalence with molar mass adjustment was based upon two-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the dose adjusted total exposure ($AUC_{ss\ 0-24\ norm}$) using an acceptance range of 80%-125%.

That method is equivalent to the two one-sided t-test procedure, each at the 5% significance level. The statistical model was an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs were calculated based on the residual error from ANOVA.

Descriptive statistics for all parameters were calculated.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 24 healthy subjects were entered into the trial and treated with at least one product.

23 subjects completed the trial per protocol. One subject withdrew consent during the second treatment period after completing the first treatment period with Lasolvan® effervescent tablets 60 mg (T2). Of the 24 entered subjects, 13 (54.2%) were male and 11(45.8%) were female. All 24 subjects were White. The age (mean and standard deviation [SD]) of the treated subjects was 25.04 (±6.423) years, weight 68.63 (±12.927) kg, and the BMI was 21.703 (±1.8476) kg/m². No important protocol violations were reported.

Efficacy / Clinical Pharmacology / Other Results:

23 treated subjects had measurable ambroxol plasma concentrations in the three treatment periods and were included in the analysis of relative bioavailability and bioequivalence of ambroxol (PK BA-set). Data of the prematurely discontinued

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subject were excluded from analysis of relative bioavailability (PK-BA set), but were included in analyses of concentration and PK parameters of ambroxol (PK-C and PK-P sets).

Relative bioavailability and bioequivalence with different molar mass

Both test formulations, T1 and T2, provided comparable peak and total exposures of ambroxol without normalisation of the daily dose in comparison to those of the reference product (R) when administered in multiple doses to healthy volunteers.

Lasolvan® prolonged-release hard capsules 75 mg (T1)

Prolonged-release hard capsules (T1) provided comparable peak exposure of ambroxol in comparison to that of the tablets (R) with the adjusted ratio of gMeans for $C_{max\ ss}$ estimated as 84.72% (90%-CI: 76.96% - 93.25%). Prolonged-release formulation (T1) provided slightly lower peak exposure of ambroxol than that of the effervescent tablets (T1 vs. T2): the adjusted ratio of gMeans for $C_{max\ ss}$ was calculated as 80.94% (90%-CI: 73.92%-88.62%).

Prolonged-release hard capsules (T1) provided similar total exposure of ambroxol without dose correction in comparison to that of tablets (R) and effervescent tablets (T2): the adjusted ratios of gMeans for $AUCss_{\ 0-24}$ were 110.68% (90%-CI: 99.84% - 122.69%) and 106.93% (90%-CI: 100.29% - 114.02%), correspondingly.

Therefore, based on the acceptance range for bioequivalence, without dose adjustment, i.e. in different molar masses, the prolonged-release hard capsules (T1) can be regarded as bioequivalent to tablets (R).

Lasolvan® effervescent tablets 60 mg (T2)

Effervescent tablets (T2) showed almost identical peak and total exposures of ambroxol in comparison to that of the tablets (R) with the adjusted ratios of gMeans for $C_{max\ ss}$ estimated as 103.87% (90%-CI: 95.22% -113.31%) and for $AUC_{ss\ 0-24}$ as 103.39% (90%-CI: 96.54% - 110.74%). Due to the identical drug

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amount used, no dose adjustment was required and thus, effervescent tablets (T2) were bioequivalent to tablets (R).

Bioequivalence based on the same molar mass

The results of the statistical assessment of bioequivalence and relative bioavailability are summarized in the Table 1.

Table 1: Analysis of relative bioavailability and bioequivalence of ambroxol after administration of Lasolvan® prolonged- release hard capsules 75 mg (T1), Lasolvan® effervescent tablets 60 mg (T2) and Lasolvan® tablets 30 mg (R) (analysis including 'subject within sequences' as random effect) (PK – BA set)

Primary endpoints	Adjusted gMean		Adjusted gMean ratio [%]	Two-sided 90% CI		Intra-individual gCV [%]
	N=23	N=23		Lower Limit[%]	Upper Limit [%]	
T1-R	**T1**	**R**				
$AUC_{ss\ 0\text{-}24}$	1184.66	1070.38	110.68	99.84	122.69	20.42
$C_{max\ ss}$	73.66	86.95	84.72	76.96	93.25	19.01
$AUC_{ss\ norm}$	947.73	1070.38	88.54	79.87	98.15	20.42
T2-R	**T2**	**R**				
$AUC_{ss\ 0\text{-}24}$	1108.80	1072.40	103.39	96.54	110.74	13.52
$C_{max\ ss}$	90.78	87.40	103.87	95.22	113.31	17.19
$AUC_{ss\ norm}$	1108.80	1072.40	103.39	96.54	110.74	13.52
T1-T2	**T1**	**T2**				
$AUC_{ss\ 0\text{-}24}$	1184.72	1107.89	106.93	100.29	114.02	12.65
$C_{max\ ss}$	73.53	90.85	80.94	73.92	88.62	17.95
$AUC_{ss\ norm}$	947.78	1107.89	85.55	80.23	91.22	12.65

Analysis including 'subject within sequences' as fixed effect displayed identical results (PK-BA set).

For the comparison T1 vs. R, bioequivalence was not demonstrated, since the adjusted ratio of gMeans for $AUC_{ss\ norm}$ was estimated as 88.54% (90%-CI:

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79.87% - 98.15%), and the lower limit of the aforementioned 90%-CI was below the pre-defined acceptance range of 80.00%.

For the comparison T2 vs. R, bioequivalence was confirmed, since both limits of the 90%-CI of the adjusted ratio of gMeans for $AUC_{ss\ norm}$ calculated as 103.39% (90%-CI: 96.54% - 110.74%) were within the pre-defined acceptance range of 80%-125%.

For the comparison T1 vs. T2, bioequivalence in terms of normalised total exposure was established. The adjusted ratio of gMeans for $AUC_{ss\ norm}$ was estimated as 85.55% (90%-CI: 80.23% - 91.22%) and both limits of the 90%-CI were within the pre-defined acceptance range of 80%-125%.

Pharmacokinetics at steady state

The results of the evaluation of the steady state PK parameters of ambroxol after administration of T1, T2 and R are summarized in Table 2.

Table 2: Steady state pharmacokinetic parameters of ambroxol after administration of T1, T2 and R

PK parameter		Mean±SD	gMean	gCV%	PK parameter		Median (min-max)	CV%
$C_{min\ ss}$, ng/mL	T1	26.674±10.480	24.891	39.355	**Tabove75%C_{max}, h**	T1	9.000 (0.00-13.00)	36.967
	T2	24.157±8.503	22.740	37.260		T2	2.250 (0.50-5.75)	53.919
	R	23.150±9.142	21.523	40.803		R	2.000 (0.50-5.25)	58.724
$C_{av\ ss}$, ng/mL	T1	51.181±14.860	49.254	28.859	**TaboveC_{av}, h**	T1	10.500 (8.00-12.50)	11.543
	T2	48.043±14.142	46.254	28.292		T2	8.500 (5.75-10.00)	11.637

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	R	46.810±15.093	44.621	32.259		R	7.750 (5.25-10.75)	14.870

Table 2: Steady state pharmacokinetic parameters of ambroxol after administration of T1, T2 and R (cont.)

PK parameter		Mean±SD	gMean	gCV%	PK parameter		Median (min-max)	CV%
PTF	T1	0.994±0.278			**Tmax ss, h**	T1	6.000 (2.00-12.00)	43.079
	T2	1.482±0.322			**Tmax 0-12 h**	T2	1.000 (0.75-3.00)	43.942
	R	1.483±0.318				R	2.000 (0.75-3.00)	31.930
PTS, %	T1	205.054±82.703			**T max 12-24 h**	T2	13.500 (12.75-16.00)	5.756
	T2	313.106±113.101				R	14.000 (13.00-16.00)	6.497
	R	322.120±135.222						

The minimum measured concentration ($C_{min\ ss}$) and average concentration at steady state ($C_{av\ ss}$), as well as their coefficients of variation, were similar across all formulations. Results obtained for other secondary pharmacokinetic parameters at steady state ($T_{max\ ss}$, PTF, PTS, T ($C>C_{av\ ss}$), T ($C>75\%C_{max\ ss}$)) confirmed further similarities between formulations T2 and R, and the differences between T1 and R, and between T1 and T2. $T_{max\ ss}$ were similar for T2 and R after the first and the second administration and differed considerably for T1. The same was true for PTF, PTS, T ($C>C_{av\ ss}$), T ($C>75\%C_{max\ ss}$) parameters.

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Safety results

Two (8.3%) subjects reported AEs during the study: one subject (4.2%) reported mild drug-related headache in the treatment period with T1, and one subject (4.2%) reported mild ALT and AST increase during the post-treatment period of T2. Liver enzymes increase was isolated. The subject reported no events of special interest in medical history. The reported liver enzymes increase might have been related to diet violation in the out-patient facility. No changes in study treatment were performed in any subject; one subject received concomitant medication to treat headache. No other (S)AE were reported. There were no clinically relevant findings with respect to safety in laboratory parameters, vital signs, or physical examination. Subjects had not clinically significant deviations from reference ranges in the results of blood chemistry and haematology that did not progress. 11 subjects had not clinically significant ECG abnormalities at baseline which did not progress during the study. There were three new episodes of incomplete right bundle branch block and one new episode of sinus bradycardia on ECG which were assessed as not clinically significant by the investigator. Study medication was assessed by investigators as well tolerated in all subjects.

Conclusions:

The investigational product Lasolvan® prolonged-release hard capsules 75 mg (T1) is bioequivalent to Lasolvan® tablets 30 mg (R) in terms of peak concentration and total exposure when different molar masses are compared.

The investigational product Lasolvan® effervescent tablets 60 mg (T2) is bioequivalent to Lasolvan® tablets 30 mg (R) in terms of peak concentration and total exposure. The comparison based on different molar masses was required for Lasolvan® prolonged-release hard capsules 75 mg (T1) because of the intrinsic release properties of this dosage form.

Ambroxol was well tolerated in all formulations when administered to healthy male and female subjects in multiple doses. No new safety issues arised from the result of the conducted study.