Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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**.

Synopsis **c09174117-01**

Name of company: Boehringer Ingelheim		**Tabulated** **Trial Report**	
Name of finished product: Mucosolvan®		**EudraCT No.:** Not applicable	
Name of active ingredient: Ambroxol hydrochloride		**Page:** 1 of 6	
Module:		**Volume:**	
Report date: 23 FEB 2012	**Trial No. / U No.:** 18.509 / c09174117-01	**Dates of trial:** 01 JUL 2011 – 23 FEB 2012	**Date of revision:** Not applicable

Title of Trial:	Relative bioavailability study between two formulations containing ambroxol hydrochloride, with administration under fasting condition in healthy volunteers of both sexes: soft pastilles test formulation of ambroxol hydrochloride 15 mg, manufactured by Bolder Arzneimittel GmbH & Co. KG and syrup reference formulation of ambroxol hydrochloride 6 mg/mL (Mucosolvan® adult syrup), manufactured by Boehringer Ingelheim Brasil Química e Farmacêutica Ltda.
Coordinating Investigator:	[redacted]
Trial sites:	[redacted] [redacted] – Brazil
Publication (reference):	Data from this trial have not been published.
Clinical phase:	Phase I (Bioequivalence study)
Objectives:	The objective of this study was to evaluate the bioavailability of ambroxol hydrochloride soft pastilles 15 mg, manufactured by Bolder Arzneimittel GmbH & Co. KG to Boehringer Ingelheim compared to ambroxol hydrochloride syrup 6 mg/mL (Mucosolvan® adult syrup), manufactured by Boehringer Ingelheim do Brasil Química e Farmacêutica Ltda.
Methodology: **Study Design**	Randomized, open label, single dose, 2-way crossover design. A single dose of medication was administered in each treatment period, followed by 48 h (2 days) of pharmacokinetic (PK) sampling. Administration of trial medication in consecutive treatment periods was separated by a minimum of 7 days' washout.

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Name of finished product: Mucosolvan®		**EudraCT No.:** Not applicable	
Name of active ingredient: Ambroxol hydrochloride		**Page:** 2 of 6	
Module:		**Volume:**	
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No. of subjects:	
planned:	36
actual:	Ambroxol hydrochloride soft pastilles 15 mg entered: 36 treated: 36 analyzed (for primary endpoint): 36 Ambroxol hydrochloride syrup 6 mg/mL entered: 36 treated: 36 analyzed (for primary endpoint): 36
Diagnosis and main criteria for inclusion	Healthy male or female subject, age 18 to 50 years, body mass index (BMI 18.5 to 29.9 kg/m^2).
Test product:	Ambroxol hydrochloride soft pastilles
Dose:	15 mg per pastilles, single dose.
Mode of admin.:	Oral
Batch no.:	2011034
Reference Therapy:	Ambroxol hydrochloride syrup 6 mg/mL
Dose:	2.5 mL (15 mg), single dose.
Mode of admin.:	Oral
Batch no.:	2952
Duration of treatment:	Single dose treatment. Each treatment was administered once in one of the 2 trial periods; each 2-day trial period was separated by a washout period of at least 7 days

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Name of finished product: Mucosolvan®		**EudraCT No.:** Not applicable	
Name of active ingredient: Ambroxol hydrochloride		**Page:** 3 of 6	
Module:		**Volume:**	
Report date: 23 FEB 2012	**Trial No. / U No.:** 18.509 / c09174117-01	**Dates of trial:** 01 JUL 2011 – 23 FEB 2012	**Date of revision:** Not applicable

Criteria for evaluation	
Clinical pharmacology	Primary endpoints were AUC_{0-t} and Cmax of ambroxol; the secondary endpoint was AUC0-∞ for ambroxol. Others pharmacokinetic parameters were tmax and t½ for ambroxol.
Safety	**SAFETY PARAMETERS** For purpose of safety follow-up, volunteers were observed during the study for detection of adverse events. In addition to events communication by the voluntary or simple observation, the investigators recorded and evaluated the following variables in order to detect adverse events: • Vital signs (Pulse, Blood Pressure and temperature) obtained during confinements (0:30, 1:30, 3:00, 5:00, 8:00, 12:00 and 24:00 hours after drug administration), and for each return to the subsequent sample collections. • Results of laboratory tests (hematology, biochemistry and urinalysis) and electrocardiogram obtained at the end of the study and evaluated in a comparative way to those obtained during the screening phase. • Physical examination findings obtained at the end of the study and evaluated in a comparative way to those obtained during the screening phase. **Post-Study procedures** All volunteers were reevaluated by subsidiary laboratory tests equal to the ones performed to the pre-study phase (excluding the serological tests).

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Name of finished product: Mucosolvan®		**EudraCT No.:** Not applicable	
Name of active ingredient: Ambroxol hydrochloride		**Page:** 4 of 6	
Module:		**Volume:**	
Report date: 23 FEB 2012	**Trial No. / U No.:** 18.509 / c09174117-01	**Dates of trial:** 01 JUL 2011 – 23 FEB 2012	**Date of revision:** Not applicable

Statistical Methods:

The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'period' and 'treatment'. Based on the residual error from the ANOVA, 2-sided 90% confidence intervals (CIs) were calculated for the ratios of the geometric means (T/R) for the primary endpoint. Bioequivalence was assessed using an acceptance range of 80.00 to 125.00% for the 90% CI. Descriptive statistics were also calculated for all endpoints.

36 subjects took 1 dose of reference product and 1 dose of test product.

36 subjects provided 1 evaluable value of reference product and 1 evaluable value of test product for the primary PK endpoints (Cmax and AUC_{0-t}) without important protocol violations with respect to the statistical evaluation of PK endpoints.

SOFTWARE USED

The statistic programs (software) used in the study: Microsoft Excel Version 97 and WinNonLin Version 5.3.

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Name of active ingredient: Ambroxol hydrochloride		**Page:** 5 of 6	Synopsis No.:
Module:		**Volume:**	
Report date: 23 FEB 2012	**Trial No. / U No.:** 18.509 / c09174117-01	**Dates of trial:** 01 JUL 2011 – 23 FEB 2012	**Date of revision:** Not applicable

SUMMARY – CONCLUSIONS

Clinical pharmacology results:

Of the 36 subjects who were entered in the trial and treated, 36 (100%) completed the planned observation time. 18 of 36 subjects (50%) were male and 18 of 36 subjects (50%) were female. Mean subject age was 30.3 years (range 19 to 49 years) and mean BMI was 24.6 kg/m^2 (range 19.5 to 29.8 kg/m^2). No subject reported relevant medical history or baseline conditions.

For the ambroxol soft pastilles 15 mg (T) compared with the ambroxol syrup 6 mg/mL (R), total (AUC_{0-t}) and peak (Cmax) ambroxol exposure was similar: mean AUC_{0-t} was 319.625 ng·h/mL for T and 269.800 ng·h/mL for R, and mean Cmax was 36.868 ng/mL for T and 32.592 ng/mL for R.

Statistical evaluation of primary endpoints (AUC_{0-t} and Cmax) for ambroxol indicated bioequivalence of both formulations (soft pastilles 15 mg and syrup 6 mg/mL). The 90% CIs for all endpoints were in the range from 80.00 to 125.00%.

Statistical evaluation of 15 mg soft pastilles (T) compared with 2.5 mL of 6 mg/mL syrup (R)

PK Parameter	Ratio of adjusted gMeans T1/R1 [%]	2-sided 90% CI [%]	Intra-indiv. gCV [%]
AUC_{0-t} [ng·h/mL]	119.61	114.65 to 124.79	10.65
Cmax [ng/mL]	113.56	106.48 to 121.10	16.24

N=36 for both T and R

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Name of active ingredient: Ambroxol hydrochloride		**Page:** 6 of 6	Synopsis No.:
Module:		**Volume:**	
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Safety results

Adverse Events (AE)

Time Frame: From drug administration (1 dose) until 48 hours for each treatment.

- Two cases of headache (subjects [redacted] and [redacted]);
- Three cases of changes in Urine I (subjects [redacted] and [redacted]);
- Two cases of change in hemoglobin exam (subject [redacted] and [redacted]);
- One case of change in Gamma GT exam (subject [redacted];
- One case of change in WBC exam (subject [redacted]).

All AE were not severe and were not expected. They had mild intensity and all AE possibly were related to ambroxol.

Including all treatment periods, 9 of 36 subjects (25%) reported an adverse event. The most frequent adverse events were headache, in 2 of 36 subjects (5.5%). There were no deaths or other serious adverse events. All adverse events had resolved by the end of the trial. Comparing across treatment periods, there were no notable differences in adverse event frequency, adverse event intensity, or relationship of adverse events to trial medication.

Mean laboratory parameters for the post-study examination (PSE) compared with screening indicated no substantial changes, except for minor changes in urine I, haemoglobin and haematology. There were no clinically relevant changes in mean laboratory parameters, individual laboratory parameters, mean vital signs, or individual vital signs over the course of the trial. The same applies to electrocardiogram (ECG) results.

Conclusions:

Statistical evaluation of AUC_{0-t} and C_{max}, for ambroxol indicated bioequivalence of the formulations. The 90% CIs for all endpoints were in the range from 80.00 to 125.00%.

At the doses used in the trial, administration of ambroxol in either soft pastilles or syrup was well tolerated in healthy volunteers.