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.:** 2009-014822-40	
Name of active ingredient: Ambroxol		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 JUN 2010	**Trial No. / U No.:** 18.493 / U10-1795-01	**Dates of trial:** 19 OCT 2009 – 24 NOV 2009	**Date of revision:** Not applicable

Title of trial:	A double-blind (at each dose level), randomised, placebo controlled phase I study to evaluate safety, tolerability and pharmacokinetics of increasing repeated oral doses of ambroxol lozenges (dosage: 20, 40, 80 mg three times daily) over 4 days in healthy male volunteers
Principal Investigator:	[redacted] Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre Clinical Operations and Biometrics and Data Management Ingelheim am Rhein, Germany
Trial sites:	Human Pharmacology Centre, Ingelheim am Rhein, Germany
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	The primary objective of the study was to determine pharmacokinetics of ambroxol after repeated oral administration of ambroxol lozenges; secondary objectives were safety and tolerability.
Methodology:	Randomised, double-blind (within treatment), placebo-controlled, multiple rising dose trial; single centre study
No. of subjects:	
planned:	Entered: 36
actual:	Entered: 34 Treatment: 20 mg ambroxol t.i.d. (Dose Group 1): entered: 9; treated: 9; analysed (for primary endpoint): 9 Treatment: 40 mg ambroxol t.i.d.(Dose Group 2): entered: 8; treated: 8; analysed (for primary endpoint): 8 Treatment: 80 mg ambroxol t.i.d. (Dose Group 3): entered: 9; treated: 9; analysed (for primary endpoint): 9 Treatment: placebo: entered: 8 (2 in Dose Group 1; 3 in Dose Group 2; 3 in Dose Group 3); treated: 8; analysed (for primary endpoint): 0

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Diagnosis and main criteria for inclusion:	Healthy male volunteers age≥21 and ≤50 years; BMI ≥18.5 and ≤29.9 kg/m^2
Test product:	Ambroxol lozenge
dose:	20 mg t.i.d.; 40 mg t.i.d.; 80 mg t.i.d.
mode of admin.:	Oral, 1 h after food intake, and followed by 150 ml water
batch no.:	918723
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral, 1 h after food intake, and followed by 150 ml water
batch no.:	09004
Duration of treatment:	Administration of ambroxol for 4 consecutive days, with 1 h between doses on Days 1 and 4 and 6 h between doses on Days 2 and 3, and with pharmacokinetic (PK) sampling on all 4 days.
Criteria for evaluation:	
Clinical pharmacology:	PK parameters of ambroxol and its metabolite 3,5-dibromoanthranilic acid (DBAA) measured in plasma and urine: Day 1: C_{max}, t_{max}, AUC_{0-24}, Ae_{0-24}, and $CL_{R,0-24}$ Day 4: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{72-96,ss}$, $Ae_{72-96,ss}$, $CL_{R,72-96,ss,}$ the accumulation ratio RA, the linearity index LI, $\lambda_{z,ss}$, and $t_{1/2,ss}$
Safety:	Physical examination, recording of vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, adverse events (AEs), and assessment of global tolerability

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Statistical methods: Dose proportionality of the PK parameters C_{max}, $C_{max,ss}$, AUC_{0-24}, $AUC_{72-96,ss}$, Ae_{0-24} and $Ae_{72-96,ss}$ were explored using a log-transformed power model. From the resulting linear regression model, the point estimate of the slope β and its 2-sided 95% confidence interval (CI) were computed for each primary parameter. For the exploration of the attainment of steady state, the trough concentrations were analysed using a mixed linear model including 'subject' as a fixed effect and 'time' as a repeated effect. Pairwise comparisons of the differences between all time points were performed using t-tests. Linearity with respect to multiple dosing using values of AUC_{0-24} and $AUC_{72-96,ss}$ was assessed employing a linear model on the logarithmic scale including 'subject' and 'order' as fixed effects. The pairwise comparison of $AUC_{72-96,ss}$ and AUC_{0-24} provided an index of linearity, for which a 2-sided 95% confidence interval was calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results: All subjects entered in the trial received all doses of trial medication and completed all trial assessments. All subjects participating in the trial were of male sex and white race. Mean age was 33.7 years and mean BMI was 25.2 kg/m^2.

Subjects' plasma exposure to ambroxol and DBAA as measured by AUC, and renal excretion of ambroxol and DBAA, were proportional to the dose of ambroxol administered. This was true for Day 1 of dosing and on Day 4 (last dose) of the trial.

Estimates of $t_{1/2}$ and renal clearance for ambroxol were similar for all dose groups, as were estimates of $t_{1/2}$ and renal clearance for DBAA. For ambroxol, gMean values of $t_{1/2}$ were 8.8 to 8.9 h and gMean values of renal clearance were 3.0 to 3.8 L/h;. for DBAA, gMean values of $t_{1/2}$ were 25.0 to 28.9 h and gMean values of renal clearance were 0.0062 to 0.0074 L/h.

For all dose groups, the accumulation of ambroxol in plasma and urine was similar and minimal over the 4 days of the study: Ratios of Day 4 to Day 1 AUC and C_{max} were 1.1 to 1.2 and ratios of Day 4 to Day 1 urinary excretion were 1.1 to 1.3. Accumulation was significantly higher for DBAA, as ratios of Day 4 to Day 1 C_{max} were 2.4 to 2.7 and ratios of Day 4 to Day 1 urinary excretion were 2.9 to 3.6.

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Safety results:	Each of the 34 subjects participating in the study each received all 12 scheduled doses of study medication (placebo or ambroxol). Total intake of ambroxol in the 20 mg t.i.d. group was 2160 mg, in the 40 mg t.i.d. group was 3840 mg, and in the 80 mg t.i.d. group was 8640 mg. There were no deaths, no serious AEs, no AEs of severe intensity, and no other significant AEs (as per ICH E3) reported. There were no pre-specified AEs defined for the study. Of the participating in the study, 11 (32% of total subjects) reported at least 1 AE. All AEs were of mild or moderate severity, and all resolved. All AEs reported occurred during the treatment phase of the study. For subjects treated with ambroxol, in the 20 mg t.i.d. group, 2 subjects (22% of the group) reported AEs; in the 40 mg t.i.d. group, 2 subjects (25% of the group) reported AEs; and in the 80 mg t.i.d. group, 4 subjects (44% of the group) reported AEs. For the ambroxol treatment groups, 5 subjects (19% of actively-treated subjects) reported AEs considered by the investigator to be related to treatment. For placebo treatment, 3 subjects (38% of the placebo group) reported AEs, and for these 3 subjects, the AEs were considered by the investigator to be related to treatment. The most common AE by system organ class was gastrointestinal disorders in 5 subjects receiving ambroxol (19% of the actively-treated group) and 2 subjects receiving placebo (25% of the placebo-treated group). No results from clinical laboratory evaluation, vital signs (systolic and diastolic blood pressure and pulse rate), or ECG analysis were considered significant by the investigator and none was reported as an AE. Global assessment of tolerability was 'good' in 25 out of 26 actively-treated subjects and in 7 of 8 subjects treated with placebo; global tolerability was 'satisfactory' in the other 2 subjects.
Conclusions:	With multiple dosing, the plasma exposure and urinary excretion of ambroxol and its major metabolite DBAA are proportional to the dose of ambroxol administered. Half-life and renal clearance of these substances are constant and independent of dose. Repeated doses of ambroxol lozenges at doses of 20 mg t.i.d, 40 mg t.i.d. or 80 mg t.i.d were safe and well tolerated in healthy male volunteers.