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***.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2006-006922-24	
Name of active ingredient: BI 11054 CL		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:** Not applicable	
Report date: 03 Nov 2009	**Trial No. / U No.:** 1250.1 / U09-2241-01	**Date of trial:** 28 Jan 2008 to 11 Aug 2008	**Date of revision** Not applicable

Title of trial:	A randomised, double-blind, placebo-controlled (within dose groups) study to assess safety, tolerability, and pharmacokinetics of single rising inhaled doses (0.5 µg to 70 µg administered with Respimat®) of BI 11054 CL in healthy male volunteers
Principal/Coordinating Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Dept. of Clinical Research / Human Pharmacology Centre, Binger Straße 173, D-55216 Ingelheim am Rhein, Germany
Publication (reference):	Data of this study has not been published.
Clinical phase:	I
Objectives:	The objective of this study was to investigate the safety, tolerability, and pharmacokinetics of treatment with BI 11054 CL single rising doses (from 0.5 µg to 70 µg) administered via inhalation with the Respimat® A5 device.
Methodology:	This was a randomised, double-blind, placebo-controlled (within each dose group), single-centre study with administration of single rising doses of BI 11054 CL.
No. of subjects:	
planned:	96
actual:	entered: 96 BI 11054 CL: entered: 72 treated: 72 (6 subjects per dose group) analysed: 72 Placebo: entered: 24 treated: 24 (2 subjects per dose group) analysed: 24
Diagnosis and main criteria for inclusion:	Healthy male volunteers, ≥21 and ≤50 years, Body Mass Index (BMI) ≥18.5 and ≤30 kg/m^2

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2006-006922-24	
Name of active ingredient: BI 11054 CL		**Page:** 2 of 4	**Synopsis No.:**
Module:		**Volume:** Not applicable	
Report date: 03 Nov 2009	**Trial No. / U No.:** 1250.1 / U09-2241-01	**Date of trial:** 28 Jan 2008 to 11 Aug 2008	**Date of revision** Not applicable

Test product:	BI 11054 CL
doses:	0.5 µg, 1.0 µg, 2.5 µg, 5.0 µg, 10 µg, 15 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, and 70 µg. These are the nominal doses and refer to the free base of the substance. One milligram BI 11054 BS (base) equals 1.070 mg BI 11054 CL (hydrochloride) (molecular weight 556.13 g/mol)
mode of admin.:	Inhalation with the Respimat® A5 device.
batch nos.:	B072000072 (0.5-2.5 µg), B072000092 (5.0-15 µg), and B072000110 (20-70 µg)
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Inhalation with the Respimat® A5 device.
batch no.:	B072000063
Duration of treatment:	One day for each treatment (single dose)
Criteria for evaluation:	
Clinical pharmacology:	C_{max}, t_{max}, AUC_{0-tz}, AUC_{t1-t2},$AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2,}$ MRT_{ih}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Safety:	The safety and tolerability of BI 11054 CL were assessed by physical examination, vital signs (blood pressure, pulse rate, respiratory rate, orthostasis test, oral body temperature), laboratory test parameters, 12-lead ECG, adverse events (AE), oropharyngeal inspection, pulmonary auscultation, airway resistance (R_{aw}), as measured by body plethysmography, and global assessment of tolerability.
Statistical methods:	Descriptive statistics were employed for safety and pharmacokinetic endpoints. A regression model with 2-sided 95% confidence interval for the slope was used to assess dose proportionality. ANCOVA was used for the analyses of the special laboratory parameters (cAMP and potassium).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2006-006922-24	
Name of active ingredient: BI 11054 CL		**Page:** 3 of 4	**Synopsis No.:**
Module:		**Volume:** Not applicable	
Report date: 03 Nov 2009	**Trial No. / U No.:** 1250.1 / U09-2241-01	**Date of trial:** 28 Jan 2008 to 11 Aug 2008	**Date of revision** Not applicable

SUMMARY – CONCLUSIONS:

Safety results:

Out of 96 subjects who were entered the trial, 72 subjects received 12 different doses of BI 11054 CL (0.5 µg to 70 µg, 6 subjects per dose group). A total of 24 subjects received placebo.

In this study, no serious adverse events, or significant AEs (according to ICH E3) were reported. Overall, 4 subjects (4.2%) reported AEs during the screening period; 26 subjects on the whole reported AEs during the treatment period with both BI 11054 CL and placebo and post-treatment period. During the treatment period, among the subjects who were administered BI 11054 CL (n=72), 16 subjects reported AEs, whereas in subjects administered placebo (n=24), 8 subjects (33.3%) reported AEs. The most frequently reported AEs among subjects who received BI 11054 CL or placebo were nervous system disorders (n=11). Most of the AEs were 'mild' in intensity except for 2 subjects (from 50 and 70 µg BI 11054 CL dose groups) who reported AEs that were 'moderate' in intensity. Mild AEs that were suspected to be treatment-related by the investigator were reported by 15 out of total 96 subjects (15.6%; 10 for BI 11054 CL and 5 for placebo treatments). Among 10 subjects who reported investigator-suspected BI 11054 CL-related AEs, no clear dose-dependency was observed. Dry mouth was observed to be the most frequent treatment-related AE reported by 4 subjects (2 subjects each for 10µg BI 11054 CL and placebo treatments) followed by restlessness in 3 subjects (one for 40µg and 2 for 70 µg BI 11054 CL) and palpitations in 3 subjects (one each for 15 µg, 50 µg BI 11054 CL and placebo treatments). All suspected treatment-related AEs were 'mild' in intensity and no concomitant medication was administered for any of these AEs. All subjects recovered from the AEs and completed the study without any discontinuations. The clinical laboratory parameters did not reveal clinically significant abnormalities. For cAMP, statistically significant treatment differences from placebo for absolute and weighted average response were observed for 5 µg dose group and all groups from the dose of 20 µg BI 11054 CL. In case of potassium, no statistically signficant differences from placebo were observed for the absolute response; but for the weighted average response, at 60 µg and 70 µg doses of BI 11054 CL, statistically significant differences from placebo were observed. No clinically relevant changes were observed for any of the vital signs parameters. An increase in HR (up to 13.8 bpm), prolongation of QTcF (up to 18.3 ms) was observed especially at higher

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2006-006922-24	
Name of active ingredient: BI 11054 CL		**Page:** 4 of 4	**Synopsis No.:**
Module:		**Volume:** Not applicable	
Report date: 03 Nov 2009	**Trial No. / U No.:** 1250.1 / U09-2241-01	**Date of trial:** 28 Jan 2008 to 11 Aug 2008	**Date of revision** Not applicable

	doses (50 µg, 60 µg and 70 µg). Airway resistance assessed by body plethysmography (mean R_{aw}) decreased from baseline only up to 8 h; the effects subsiding between 8 and 24 h after drug administration. Examinations of the oropharynx and the pulmonary auscultations during the course of the study did not suggest any notable adverse effect induced by BI 11054 CL treatment. The investigator assessed the overall tolerability as 'good' for 92 out of 96 subjects and as 'satisfactory' for 4 subjects (3 for 15 µg BI 11054 CL and one for placebo).
Clinical pharmacology results:	<u>Pharmacokinetics:</u> Following single inhalation of 0.5 µg and 1.0 µg BI 11054 CL, plasma concentrations of BI 11054 BS were too low to be detected. In the subjects treated with 2.5–70 µg BI 11054 CL maximum drug plasma concentrations were measured 7 to 33 min after drug inhalation (t_{max} range: 0.117–0.550 h, median: 0.217 h). Plasma concentrations thereafter declined with an at least bi−exponential disposition kinetics. The overall gMean terminal half-life $t_{1/2}$ was 6.17 h with moderate inter-individual variability (gCV 36.1%). Excretion of unchanged BI 11054 BS in urine accounted for approximately 7% of the BI 11054 CL dose. Renal clearance ($CL_{R,0-24}$) of BI 11054 BS was 92.3−129 mL/min in the dose groups 40 µg to 70 µg BI 11054 CL, with no obvious trend related to the dose. Based on C_{max}, AUC_{0-2} and $AUC_{0-\infty}$ values, and urinary excretion data, BI 11054 BS after inhalation via the Respimat® inhaler exhibits dose-proportional pharmacokinetics within the dose-range 2.5–70 µg BI 11054 CL.
Conclusions:	The single rising doses of BI 11054 CL were safe and well tolerated up to the dose of 70 µg by healthy male subjects. Typical β_2-adrenoceptor agonist-related pharmacodynamic effects were observed in subjects starting at doses of 20 µg BI 11054 CL. Based on C_{max}, AUC_{0-2} and $AUC_{0-\infty}$ values and urinary excretion data it can be concluded that BI 11054 BS after inhalation via the Respimat® inhaler exhibits linear pharmacokinetics within the dose-range 2.5–70 µg BI 11054 CL. The disposition kinetics was at least bi-exponential, with a terminal elimination half-life of approximately 6 h.