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:		**EudraCT No.:** 2008-007340-34	
Name of active ingredient: BI 1744 CL and BI 54903 XX		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 23 FEB 2010	**Trial No. / U No.:** 1256.2 / U10-1238-01	**Dates of trial:** 31 MAR 2009 – 26 JUN 2009	**Date of revision:** Not applicable

Title of trial:	A single-blind, randomised, two-way crossover Phase I study to asses safety, tolerability and pharmacokinetics of the fixed dose combination of BI 1744 CL plus BI 54903 XX via Respimat® B versus the free combination of BI 1744 CL via Respimat® A and BI 54903 XX via Respimat® B in healthy male and female volunteers
Principal Investigator:	[redacted]
Trial sites:	Boehringer Ingelheim Pharma GmbH & Co. KG Dept. of Clinical Research/Human Pharmacology Centre Ingelheim, Germany
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	The primary objective of this study was to compare the systemic exposure of BI 1744 BS and CD 1857 XX (the active metabolite of the pro-drug BI 54903 XX) at steady state following inhalation of the fixed dose combination (FDC) of 6.2 µg BI 1744 CL plus 727.3 µg BI 54903 XX (as ethanolic solution for inhalation, EIS) with the systemic exposure following inhalation of the free dose combination of 10 µg BI 1744 CL (as aqueous solution for inhalation, AIS) and 727.3 µg BI 54903 XX (EIS), respectively, when administered once-daily via Respimat® Inhaler (Respimat® A for AIS and Respimat® B for EIS) for 14 days in healthy volunteers. Secondary objectives were: to compare exposure to BI 1744 BS and CD 1857 XX after a single dose of the BI 1744 CL/BI 54903 XX (6.2 µg/727.3 µg) FDC and the free dose combination, respectively; to compare exposure to BI 54903 XX after a single dose and at steady state after multiple doses of the BI 1744 CL/BI 54903 XX (6.2 µg/727.3 µg) fixed dose combination and the free dose combination, respectively; to compare the safety and tolerability of BI 1744 CL and BI 54903 XX when administered as BI 1744 CL/BI 54903 XX (6.2 µg/727.3 µg) fixed dose combination and as the free dose combination, respectively.
Methodology:	Single-blind, randomised, two-way crossover

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No. of subjects:	
planned:	entered: 32 subjects (30 completed subjects intended)
actual:	Treatment A: entered: 32 treated: 32 analysed (for primary endpoint): 31 Treatment B: entered: 32 treated: 32 analysed (for primary endpoint): 31
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥21 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	Treatment B: • BI 1744 CL and BI 54903 XX FDC as EIS via Respimat® B • Placebo as AIS via Respimat® A
dose:	6.2 µg BI 1744 CL and 727.3 µg BI 54903 XX, q.d. over 14 days
mode of admin.:	Inhalation via the Respimat® A and B Inhaler
batch no.:	FDC: B082000257 (cartridge) and B082000276 (device) Placebo: B082000136 (cartridge) and B072000350 (device)
Reference therapy:	Treatment A: • BI 1744 CL as AIS via Respimat® A • BI 54903 XX as EIS via Respimat® B
dose:	10 µg BI 1744 CL and 727.3 µg BI 54903 XX, q.d. over 14 days
mode of admin.:	Inhalation via the Respimat® A and B Inhaler
batch no.:	AIS: B072000356 (cartridge) and B072000354 (device) EIS: B082000232 (cartridge) and B082000195 (device)
Duration of treatment:	Two treatment periods of 14 days separated by a wash-out period of at least 20 days

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Criteria for pharmacokinetics:	Primary endpoints: • $C_{max,ss}$ and $AUC_{0-t,ss}$ for BI 1744 BS and CD 1857 XX Secondary endpoints: • $C_{max,ss}$ and $AUC_{0-t,ss}$ for BI 54903 XX • single dose PK parameters and further steady state PK parameters for BI 1744 BS, CD 1857 XX and BI 54903 XX
Criteria for Safety:	Medical examination, pulse rate, blood pressure, 12-lead ECG, laboratory parameters, adverse events (AEs), and assessment of global tolerability.
Statistical methods:	Confidence intervals, analysis of variance, descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy/clinical pharmacology results:

BI 1744 BS

Maximum plasma concentrations of BI 1744 BS after single as well as after multiple inhalations of either the free or the fixed dose combination were observed at 12–16 minutes after the inhalation. Plasma concentrations declined rapidly and at least bi-exponentially thereafter. The time point of the last quantifiable plasma concentration (t_z) was highly variable, and ranged between 12 minutes and 4 h after single inhalation and between 17 minutes and 24 h after multiple inhalations. Accumulation of BI 1744 BS in plasma after multiple once daily administrations based on C_{max} values accounted for a factor of 1.14–1.25 (gMean $R_{A,Cmax}$; gCV: 32.0%).

Statistical comparison of the fixed dose combination (test) with the free combination (reference) by analysis of variance (ANOVA) revealed adjusted geometric mean test/reference ratios of 120% for $C_{max,ss}$ (90% confidence interval CI: 109–131%) and 118% for $AUC_{0-0.75,ss}$ (representing $AUC_{0-t,ss}$; CI: 106-–132%). For $AUC_{0-1,ss}$ (secondary endpoint, since available from less than two thirds of the treated subjects) the adjusted gMean test/reference ratio was 110% (CI: 98–124%).

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Efficacy/clinical pharmacology results (continued):

CD 1857 XX

Maximum plasma concentrations of CD 1857 XX after single as well as after multiple inhalations of either the free or the fixed dose combination were observed at 12–13 minutes after the inhalation. Concentrations declined thereafter in an at least bi-exponential manner with an initial phase up to ~6 h and a second phase thereafter. The geometric mean terminal elimination half-life as determined from the steady state plasma concentration profiles ($t_{½,ss}$) was 9.73 h (free combination; gCV:14.0%) and 9.92 h (FDC; gCV: 19.8%). Accumulation of CD 1857 XX in plasma after multiple once daily administrations based on C_{max} and AUC_{0-8} values accounted for a factor of 1.07–1.18 (gMean $R_{A,Cmax}$ and $R_{A,AUC0-8;}$ gCV: 15.1–33.2%). Metabolite-to-parent ratios at steady state ($RAUC_{\tau,ss,Met}$) were 123% (gCV: 20.0%, free combination) and 120% (gCV: 20.6%, FDC). Statistical evaluation of $C_{max,ss}$, $AUC_{0-8,ss}$ (primary endpoints), and $AUC_{\tau,ss}$, $AUC_{0-tz,ss}$, C_{max}, AUC_{0-8}, AUC_{0-tz} (secondary endpoints) by ANOVA revealed adjusted geometric mean test/reference ratios of 96–106%, with 90% confidence intervals all completely located within the generally applied bioequivalence acceptance limits of 80–125%.

BI 54903 XX

Maximum plasma concentrations of BI 54903 XX after single as well as after multiple inhalations of either the free or the fixed dose combination were observed at 4–7 minutes after the inhalation. Concentrations thereafter declined in a multi-exponential manner. The geometric mean terminal elimination half-life as determined from the steady state plasma concentration profiles ($t_{½,ss}$) was 10.7 h (free combination; gCV: 34.8%) and 11.7 h (FDC; gCV: 53.0%). Accumulation of BI 54903 XX in plasma after multiple once daily administrations based on C_{max} and AUC_{0-6} values accounted for a factor of 0.961–1.13 (gMean $R_{A,Cmax}$ and $R_{A,AUC0-6;}$ gCV: 20.8–28.0%).

Statistical evaluation of $C_{max,ss}$, $AUC_{0-8,ss}$, $AUC_{\tau,ss}$, $AUC_{0-tz,ss}$, C_{max}, AUC_{0-6}, and AUC_{0-tz} (all as secondary endpoints) by ANOVA revealed adjusted geometric mean test/reference ratios of 96–113%, with 90% confidence intervals all completely located within the generally applied bioequivalence acceptance limits of 80–125%.

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Safety results:

Over the course of the study, all subject received all planned doses of BI 1744 CL and BI 54903 XX, resulting in a total dose of 226.8 µg BI 1744 CL and 20.4 mg BI 54903 XX per subject.

In total 18 subjects (56.3%) reported AEs during the course of the study. All reported AE episodes were recovered until the end of the trial and no subject was discontinued due to an AE. There was no SAE reported in this trial. All AEs were of mild or moderate intensity. The most frequently reported AEs in the treatment and washout phases by system organ class were 'nervous system disorders' (8 subjects, 25.0%), 'respiratory, thoracic and mediastinal disorders' (6 subjects, 18.8%) and 'infections and infestations' (4 subjects, 12.5%).

The overall number of subjects reported with AEs was comparable between the 2 treatments. Six subjects reported a total of 9 AEs that were assessed as treatment-related by the investigator. All of the related events were known effects of either the investigational drugs or the inhalative route of administration. None of the related events required therapy.

Clinical laboratory tests and the evaluation of vital signs and ECG revealed no safety issues in this study.

Conclusions:

Systemic bioavailability of CD 1857 XX and BI 54903 XX from the fixed dose combination was equivalent to the free combination. For BI 1744 BS 18 to 20% higher $C_{max,ss}$ and $AUC_{0-0.75,ss}$ values after inhalation of the fixed dose combination as compared to the free combination however suggest formulation dependent higher bioavailability from the ethanolic FDC than from the aqueous BI 1744 CL mono solution.

The free dose combination of 727.3 µg BI 54903 XX and 10 µg BI 1744 CL once daily over 14 days as well as the fixed dose combination of 727.3 µg BI 54903 XX and 6.2 µg BI 1744 CL once daily over 14 days were safe and well tolerated in healthy volunteers and no meaningful difference was observed in the safety profiles of the free and fixed dose combination.