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:		**EudraCT No.:** 2008-007341-31	
Name of active ingredient: BI 1744 CL and BI 54903 XX		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 23 APR 2010	**Trial No. / U No.:** 1256.3 / U10-1611-01	**Dates of trial:** 01 APR 2009 - 23 JUL 2009	**Date of revision:** Not applicable

Title of trial:	An open label, randomised, three-way crossover Phase I study to assess safety, tolerability and pharmacokinetics of the fixed dose combination of BI 1744 CL plus BI 54903 XX via Respimat® B versus the mono products 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 am Rhein, 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 mono compounds 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 mono compounds, 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) FDC and the mono compounds, 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) FDC and as the mono compounds, respectively.
Methodology:	Open label, randomised, three-way crossover

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No. of subjects:	
planned:	entered: 36 (30 completed subjects intended)
actual:	Treatment A: FDC entered: 36 treated: 36 analysed (for primary endpoint): 36 Treatment B: BI 1744 CL entered: 36 treated: 36 analysed (for primary endpoint): 36 Treatment C: BI 54903 XX entered: 36 treated: 36 analysed (for primary endpoint): 36
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥21 and ≤50 years, body mass index range: ≥18.5 and ≤29.9 kg/m^2
Test product:	Treatment A: BI 1744 CL/BI 54903 XX FDC as EIS via Respimat® B
dose:	6.2 µg BI 1744 CL and 727.3 µg BI 54903 XX, once daily over 14 days
mode of admin.:	Oral inhalation via the Respimat® B Inhaler
batch no.:	B082000257 (cartridge) and B082000276 (device)
Reference therapy:	Treatment B: BI 1744 CL as AIS via Respimat® A
dose:	10 µg BI 1744 CL, once daily over 14 days
mode of admin.:	Oral inhalation via the Respimat® A Inhaler
batch no.:	B072000356 (cartridge) and B072000354 (device)
Reference therapy:	Treatment C: BI 54903 as EIS via Respimat® B
dose:	727.3 µg BI 54903 XX, once daily over 14 days
mode of admin.:	Oral inhalation via the Respimat® B Inhaler
batch no.:	B082000232 (cartridge) and B082000195 (device)

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Duration of treatment:	Three treatment periods of 14 days separated by wash-out periods of at least 20 days
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:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, laboratory tests, adverse events (AEs) and assessment of global tolerability
Statistical methods:	Confidence intervals, analysis of variance (ANOVA), descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The study population consisted of 36 healthy volunteers, 24 male and 12 female. All subjects were white with an age ranging from 21 to 46 years (mean: 36.6, SD: 7.0 years) and a body mass index of 19.5 to 29.7 kg/m2 (mean: 24.37, SD: 2.84 kg/m2). No relevant medical history or baseline conditions were reported for any of the participating subjects. All subjects completed all 3 treatment phases and the end-of trial follow up; there was no important protocol violation reported in this trial.

<u>BI 1744 BS</u>

Maximum plasma concentrations of BI 1744 BS after single as well as after multiple inhalations of either the mono compound or the FDC were observed at 10–15 min 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 10 min and 3 h after single inhalation and between 15 min 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 1.40–1.43 (gMean $R_{A,Cmax}$; gCV: 21.9% [FDC] and gCV: 33.4% [mono compound]). Steady state, based on a statistical evaluation of the amounts of BI 1744 BS excreted in urine, was attained on Day 6.

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Efficacy / clinical pharmacology results (continued):

Statistical comparison of the FDC (test) with the mono compound (reference) revealed for the primary endpoints adjusted geometric mean test/reference ratios of 127.0% for $C_{max,ss}$ (90% confidence interval CI: 117.5–137.4%) and 113.8% for $AUC_{0-3,ss}$ (representing $AUC_{0-t,ss}$; CI: 107.0–121.0%). In conclusion, considering also the secondary endpoints, for most of the parameters the 90% CI exceeds the accepted bioequivalence limits of 80-125%, suggesting a higher systemic exposure from the ethanolic FDC than from the aqueous mono solution.

CD 1857 XX

Maximum plasma concentrations of CD 1857 XX after single as well as after multiple inhalations of either the BI 54903 XX mono compound or the FDC were observed at 10 min 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 10.3 h (FDC; gCV: 24.9%) and 9.83 h (mono compound; gCV: 20.4%). Accumulation of CD 1857 XX in plasma following multiple once daily administrations based on C_{max} and AUC_{0-8} values accounted for a factor of 1.05–1.17 (gMean $R_{A,Cmax}$ and $R_{A,AUC0-8}$; gCV: 16.5–23.1%). Metabolite-to-parent ratios at steady state ($R_{AUC\tau,ss,Met}$) were 134% (gCV: 26.5%, FDC) and 143% (gCV: 25.6%, mono compound). Steady state, based on statistical evaluation of trough plasma samples, was attained on Day 7. Urinary excretion of CD 1857 XX after single and multiple inhalations of either the BI 54903 XX mono compound or the FDC was negligible.

Statistical evaluation of $C_{max,ss}$ and $AUC_{\tau,ss}$ revealed adjusted geometric mean test/reference ratios of 101.9% (CI: 95.4-108.8%) and 95.2% (91.3-99.3%), respectively, with 90% confidence intervals all completely located within the generally applied bioequivalence acceptance limits of 80–125%. Therefore an equivalent systemic exposure at steady state after the inhalation of the FDC and the BI 54903 XX mono compound was assumed for the active metabolite of BI 54903 XX. Statistical evaluation of the secondary endpoints AUC_{0-8}, AUC_{0-tz} and C_{max} revealed adjusted geometric mean test/reference ratios of 87.8 to 100.8%, with 90% confidence intervals all completely located within the generally applied bioequivalence acceptance limits of 80–125%.

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Efficacy / clinical pharmacology results (continued):	BI 54903 XX Maximum plasma concentrations of BI 54903 XX after single as well as after multiple inhalations of either the mono compound or the FDC were observed at 3.0–4.5 min 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 11.6 h (FDC; gCV: 58.9%) and 9.88 h (mono compound; gCV: 46.9%). 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 0.894–1.05 (gMean $R_{A,Cmax}$ and $R_{A,AUC0-6}$; gCV: 21.0–36.6%). BI 54903 XX was not detectable in urine after single and multiple inhalations of either the BI 54903 XX mono compound or the FDC. 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) revealed adjusted geometric mean test/reference ratios of 91.2 to 106.4%, with 90% confidence intervals all completely located within the generally applied bioequivalence acceptance limits of 80-125%.
Safety results:	Over the course of the study, all but 2 subjects received all planned doses of BI 1744 CL and BI 54903 XX. The mean total dose of BI 1744 CL was 226.1 µg (SD: 5.1) and the mean total dose of BI 54903 XX was 20.38 mg (SD: 0.12). The mean total treatment duration was 41.9 days (SD: 0.5), resulting in a total of 1510 days of exposure for all subjects over the course of the study. In total 28 subjects (77.8%) reported AEs during the course of the study. 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 by system organ class were 'nervous system disorders' (15 subjects, 41.7%), 'infections and infestations' (11 subjects, 30.6%), 'gastrointestinal disorders (7 subjects, 19.4%), 'respiratory, thoracic and mediastinal disorders' and 'musculoskeletal and connective tissue disorders' (6 subjects each, 16.7%). The overall number of subjects reported with AEs was comparable between the 3 treatments.

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Safety results (continued):	Seven 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. The global tolerability was rated as good for all subjects.
Conclusions:	Systemic bioavailability of BI 54903 XX and its active metabolite CD 1857 XX after once daily inhalation of a FDC of 6.2 µg BI 1744 CL and 727.3 µg BI 54903 XX over 14 days was equivalent to the application as mono compound (727.3 µg BI 54903 XX). For BI 1744 BS 14-27% higher $AUC_{0-3,ss}$ and $C_{max,ss}$ values after inhalation of the FDC as compared with the mono compound (10 µg BI 1744 CL) suggest higher bioavailability from the ethanolic FDC than from the aqueous mono solution. The mono compounds of 727.3 µg BI 54903 XX or 10 µg BI 1744 CL as well as the FDC 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 mono compounds and the FDC.