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 Study Report**		
Name of finished product: -				
Name of active ingredient: BEA 2180 BR		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 21 DEC 2004	**Number:** U04-2144-01	**Study period (dates):** 27 Aug 03 – 09 Jun 04		**Revision date:** 15 Nov 05

Title of study:	Safety, tolerability, pharmacodynamics and pharmacokinetics of single rising inhaled BEA 2180 BR doses (2.5 µg to 1600 µg administered with the Respimat®) in healthy male subjects, alone and followed by methacholine challenge. A randomised, double-blind within dose group, placebo-controlled study, with a 36 µg tiotropium bromide single dose sub-study (open, two-fold crossover). The sub-study is reported separately (CTR 1205.9001)
Investigator:	[redacted]
Study center:	Boehringer Ingelheim Pharma GmbH & Co. KG Dept. of Clinical Research / Human Pharmacology Center Binger Str. 173 55216 Ingelheim/Rhein, Germany Phone: [redacted] Fax: [redacted]
Publication (reference):	Data of this study so far has not been published
Clinical phase:	I
Objectives:	To investigate safety, tolerability, PD and PK of BEA 2180 BR
Methodology:	Main study: randomised, double-blind (within dose group), placebo controlled within dose group, single rising dose, repetition of dose after at least two weeks washout (dose groups 15 µg and higher)
No. of subjects:	
planned:	To be entered: main study: 93
actual:	To be entered: main study: 90
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 30 – 55 years, BMI range: 18.5 to < 30 kg/m^2
Test product main study:	BEA 2180 BR solution for inhalation with the Respimat®
dose:	2.5 µg, 5 µg, 15 µg, 50 µg, 100 µg, 200 µg, 400 µg, 700 µg, 1000 µg, 1300 µg, 1600 µg (calculated as BEA 2180 cation delivered dose)
mode of admin.:	Inhalation of BEA 2180 BR solution with the Respimat®

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batch no.:	Inhalation solution 2.5 µg BEA 2180 per actuation: cartridge 0304201, Respimat® WE01080199 Inhalation solution 10 µg BEA 2180 per actuation: cartridge 0305201, Respimat® WE01080199 Inhalation solution 100 µg BEA 2180 per actuation: cartridge 0304203, Respimat® WE01080199
Duration of treatment (test product):	One day (single dose) for each treatment. Dose groups 15 µg BEA 2180 and higher except 700 µg BEA 2180 dose group : one single dose alone and one single dose followed by methacholine challenge
Training device main study:	Placebo solution for inhalation with the Respimat®
dose:	-
mode of admin.:	Inhalation of placebo solution with Respimat®
batch no.:	Respimat®: WE01080199 Placebo solution: 203154
Reference therapy:	Placebo solution for inhalation with the Respimat®
dose:	-
mode of admin.:	Inhalation of placebo solution with the Respimat®
batch no.:	Inhalation solution placebo: cartridge 0303201, Respimat® WE01080199
Duration of treatment (reference product):	One day (single dose) for each treatment. Dose groups 15 µg BEA 2180 and higher except 700 µg BEA 2180 dose group : one single dose alone and one single dose followed by methacholine challenge
Criteria for evaluation:	
Efficacy:	Pharmacodynamics: airway resistance (R_{aw}) and specific conductance (sG_{aw}) alone and with methacholine challenge, Pharmacokinetics: AUC_{0-4h}, AUC_{0-24}, AUC_{0-tz}, C_{max}, $C_{0.083}$, C_2, C_{24}, t_{max}, Ae_{0-4}, Ae_{0-24}, Ae_{0-312}, fe_{0-4}, fe_{0-24}, fe_{0-312}, $CL_{R,0-4h}$ (λ_Z, $t_{1/2}$, $AUC_{0-\infty}$, MRT_{inh}, CL/F, CL_{R0-24}, $CL_{R,0-240}$ V_z/F if reasonable, and $C_{0.083}$, C_2, and Ae_{0-24}, fe_{0-24} on day with methacholine challenge)

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Safety: Physical examination, vital signs (BP, PR, RR, oral body temperature, orthostase test), pulmonary auscultation, ECG, salivary secretion, pupillometry (only in the next higher dose group after a 50% decline of salivary secretion was observed), oropharyngolaryngeal inspection, pulmonary function, laboratory tests, adverse events and tolerability.

Statistical methods: Descriptive statistics and confidence intervals of changes to baseline, frequencies of events.

SUMMARY – CONCLUSIONS:

Efficacy results:
Pharmacodynamic effects

Effects on airway resistance (body plethysmography): mean values (difference to baseline) for R_{aw} for the treatment groups placebo and 2.5µg BEA 2180 showed almost no changes. For all other doses from 5 µg BEA 2180 onwards, numerically but consistently a decrease of R_{aw} was observed at all time-points measured.

Inhibition of methacholine challenge: during the screening phase all R_{aw} ratios (challenge/baseline value) were between 2 and 3 indicating that the methacholine provocation was successful. Figure 1 demonstrates that subjects treated with placebo are clearly separated from subjects treated with active drug. For doses 15 µg and 50 µg BEA 2180, the methacholine test was performed 1 h after treatment. Airway protection versus methacholine of these two doses after 1 h could be demonstrated. For doses 100 µg BEA 2180 and higher, the methacholine test was performed after 24 h and again airway protection versus methacholine was demonstrated.

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Efficacy results (con.):

Bronchodilatory and bronchoprotective effects

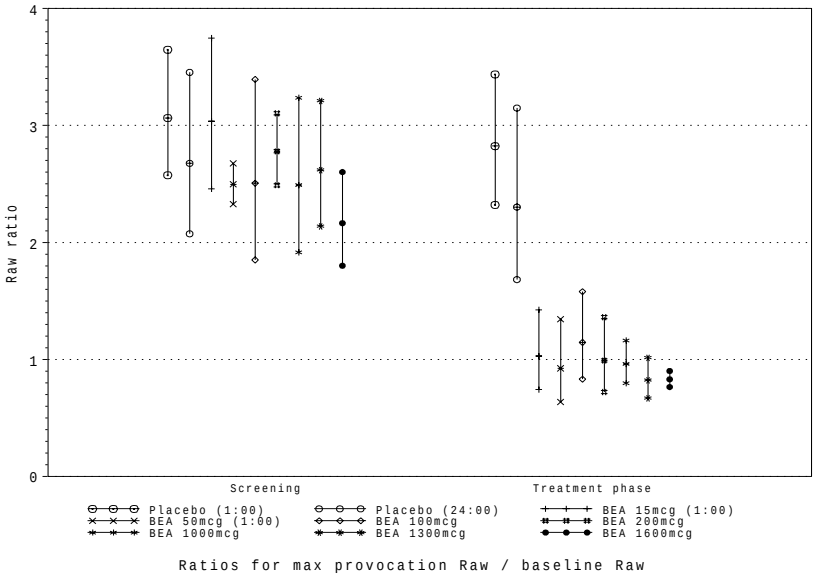

Figure 1: Results of methacholine test (gMeans and gSDs of ratios for R_{aw})

Conclusion of pharmacodynamic effects

Based on evaluation of numerical changes in R_{aw}, 2.5 µg BEA 2180 induced no effects. Five and fifteen microgramm BEA 2180 or higher numerically but consistently reduced airway resistance which may indicate anticholinergic effects in the airways. Methacholine challenge was inhibited after 24 h by BEA 2180 at doses of 100 µg and higher. For doses 15 µg and 50 µg protection against methacholine challenge was shown after 1 hour (24 h post dose methacholine challenge was not performed in these dose groups).

Pharmacokinetic results

BEA 2180 BR was rapidly absorbed after inhalation (t_{max} about 5 min). Maximum plasma concentrations could not be determined accurately due to the fast rise and decline in plasma concentrations and the different time duration required for inhalation (start time of PK sampling was the end of inhalation of 1-16 puffs). This resulted in a high variability in C_{max}. Therefore, C_{max} was not used for assessment of dose-linearity.

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Efficacy results (con.):
Pharmacokinetics

BEA 2180 exhibits at least bi-exponential disposition pharmacokinetics. BEA 2180 plasma concentrations declined rapidly to about one-tenth of the maximum plasma concentration within the first 2 hours after inhalation. Beyond 24 hours, plasma concentrations declined in a relatively stable terminal phase up to 240 hours after inhalation (terminal half-life $t_{1/2}$ about 86 hours or 3.6 days). Based on AUC_{0-24} and $AUC_{0-\infty}$, it can be concluded that BEA 2180 exhibits dose-linear pharmacokinetics within the dose range tested. Overall pharmacokinetic parameters were calculated for the 100 µg to 400 µg and 1600 µg dose groups: overall total clearance (CL/F) was moderate with about 1890 mL/min and showed low to moderate variability (34.9 gCV). The overall volume of distribution during the terminal phase (V_z/F) was high (14000 L, with 36.6 % gCV). Renal clearance of the drug was about 280 mL/min and exceeded the glomerulary filtration rate (GFR ~ 125 mL/min). Therefore, BEA 2180 was also actively secreted. After inhalation of anticipated therapeutic doses of BEA 2180 (15-400 µg), about 12 % of the dose were renally excreted within 13 days after inhalation. Renal excretion was almost complete after 13 days. However, less than 5 % of the inhaled dose were excreted in urine within the first 24 hours after inhalation. The isoenzyme CYP 2D6 did not seem to have a significant influence on the metabolism of BEA 2180.

Conclusion of pharmacokinetic results

Based on evaluation of AUC values, BEA 2180 showed dose-linear pharmacokinetics. The moderate clearance and high volume of distribution resulted in a long terminal half-life of about 3.6 days. About 12 % of the dose were excreted unchanged in urine. The isoenzyme CYP 2D6 did not seem to have a major impact on the metabolism of BEA 2180.

Safety results:

Inhalation of single doses of 2.5 µg to 1600 µg BEA 2180 was safe and well tolerated. Tussive irritation was observed in few subjects at high doses. No reduction of salivary secretion at and well beyond the anticipated therapeutically relevant doses could be detected. Repeated evaluation during the course of the study of laboratory, ECG, lung function (as assessed by bodyplethysmography), vital parameters (including systolic/diastolic blood pressure, heart rate, respiratory rate and orthostasis test), as well as multiple examinations of the larynx and oropharynx, pulmonary auscultation and neurological assessments did not suggest adverse drug reactions.

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Conclusions:	Single inhaled doses of BEA 2180 BR were safe and well tolerated from 2.5 µg to 1600 µg BEA 2180. Mild tussive irritation was reported by some subjects from the 400 µg dose onwards. Airway resistance was lowered already with 5 µg BEA 2180 two to six hours following administration. Reduced resistance was still demonstrable at 24 h post dosing after the 100 µg BEA 2180 and higher doses. No signs of paradoxical or delayed bronchoconstriction were seen even with highest dose