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: 06 JUL 2005	**Number:** U05-1793-01	**Study period (dates):** 25 May 04 - 15 Feb 05		**Revision Date:** 07 Nov 2005

Title of study:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising inhalative doses (20 µg, 50 µg, 100 µg, 200 µg, and 400 µg) of BEA 2180 BR for 21 days in healthy male volunteers (double-blind, randomised, placebo controlled [at each dose level] study)
Investigator:	[redacted]
Study center:	Boehringer Ingelheim Pharma GmbH & Co. KG Dept. of Clinical Research / Human Pharmacology Centre 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 and tolerability, PD and PK of BEA 2180 BR
Methodology:	Multiple rising inhalative doses (20 µg, 50 µg, 100 µg, 200 µg, and 400 µg) of BEA 2180 BR for 21 days in healthy male volunteers (double-blind, randomised, placebo controlled [at each dose level] study)
No. of subjects: **planned:** **actual:**	 entered: 60 enrolled: 59
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 30- 55 years, BMI range: 18.5 to < 30 kg/m²
Test product: **dose:** **mode of admin.:** **batch no.:**	BEA 2180 solution for inhalation with the Respimat® 20 µg, 50 µg, 100 µg, 200 µg, 400 µg Inhalation with the Respimat® BEA 2180 solution for inhalation - 10 µg BEA 2180- batch-no: 0401202 BEA 2180 solution for inhalation - 100 µg BEA 2180- batch-no: 0401203 Respimat®: 3U 0044
Duration of treatment:	One daily dose for 21 days

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Training device:	Placebo solution for inhalation with the Respimat®
dose:	-
mode of admin.:	Inhalation with the Respimat®
batch no.:	Placebo solution for inhalation: 0401201 Respimat®: 3U 0044
Reference therapy:	Placebo solution for inhalation with the Respimat®
dose:	-
mode of admin.:	Inhalation with the Respimat®
batch no.:	Placebo solution for inhalation: 0401201 Respimat®: 3U 0044
Efficacy:	Pharmacokinetic parameters: C_{max}, t_{max}, AUC_{0-24}, AUC_{0-tz}, Ae_{0-24}, fe_{0-24}, $CL_{R,\ 0-24,}$ $C_{pre,ss}$, $C_{max,ss}$, $C_{min,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, $Ae_{\tau,ss}$, $fe_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss,}$ $CL_{R,ss}$, $MRT_{ih,ss}$, R_A, PTF
Safety:	Physical examination, vital signs (BP, PR), body plethysmography (R_{eff} and SG_{eff}), salivary secretion, ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistics for safety. PD and PK endpoints will be calculated. Dose proportionality will be explored using mainly graphically methods.

SUMMARY – CONCLUSIONS:

Efficacy results:

Based on evaluation of numerical changes in R_{aw}, all BEA 2180 doses showed effects. BEA 2180 dose groups 100 µg, 200 µg, and 400 µg are clearly separated from the other treatment groups through all time-points measured. BEA 2180 dose groups 20 µg and 50 µg are also separated from placebo on test days 1 and 21 (for test day 21 not on trough), but not when looking at trough values.

Protection against methacholine challenge was shown for all BEA 2180 doses on day 22 and all doses are separated from placebo.

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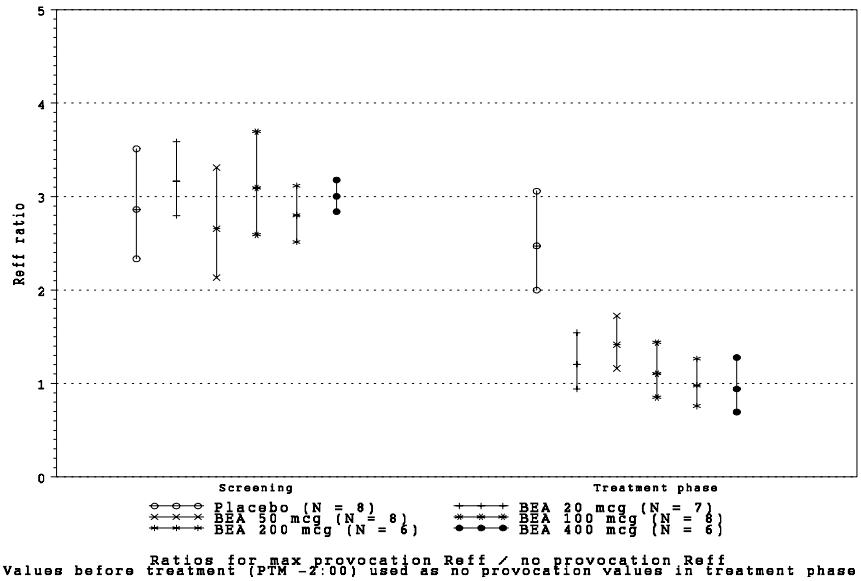

Source data: Tables 15.2.1.1: 2

Figure 1 Results of MCh test (gMeans and gRange of ratios for Raw)

Pharmacokinetics:

After single and multiple dose inhalations of BEA 2180 BR, maximum plasma concentrations of BEA 2180 were reached within 2-5 min after inhalation. Plasma concentrations declined rapidly within the first 2 h. Beyond 24 h after the last inhalation, plasma concentrations declined in a relatively stable terminal phase up to 336 h. With once daily dosing, predose plasma concentrations approached a plateau after 8 days, and steady state was reached within 14 days of treatment. Maximum concentrations, AUC and amounts of BEA 2180 excreted unchanged in urine over the dosing interval on days 1 and 21 with the respective accumulation ratios are given in the Table below:

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		20 µg gMean (% gCV)	50 µg gMean (% gCV)	100 µg gMean (% gCV)	200 µg gMean (% gCV)	400 µg gMean (% gCV)
C_{max}	**[pg/mL]**	10.8 (85.0)	33.3 (47.9)	113 (63.5)	321 (101)	1140 (45.3)
$C_{max,ss}$	**[pg/mL]**	20.4 (45.1)	38.7 (39.3)	115 (33.0)	401 (42.3)	1000 (92.2)
RA_{Cmax}		2.07 (64.3)	1.25 (44.5)	1.08 (50.8)	0.897 (37.5)	0.814 (70.3)
AUC_{0-24}	**[pg·h/mL]**	NC	143 (12.9)	216 (31.8)	605 (55.0)	1090 (45.6)
$AUC_{\tau,ss}$	**[pg·h/mL]**	162 (37.0)	311 (35.4)	690 (27.7)	2310 (30.4)	2700 (66.6)
RA_{AUC}		NC	2.18 (28.9)	3.25 (41.5)	3.14 (24.4)	2.32 (30.2)
Ae_{0-24}	**[µg]**	709 (32.3)	1560 (40.7)	3490 (40.0)	9940 (54.5)	17900 (53.2)
$Ae_{\tau,ss}$	**[µg]**	2960 (39.9)	4970 (35.5)	12200 (28.2)	40000 (34.1)	44700 (75.0)
RA_{Ae}		4.46 (49.6)	2.86 (36.8)	3.64 (37.9)	3.26 (19.1)	2.22 (35)

Source data: Tables 15.5.2.1: 1-10

Based on visual inspection of AUC_{0-24} and $AUC_{\tau,ss}$, BEA 2180 exhibits dose-linear pharmacokinetics within the dose range tested. Overall pharmacokinetic parameters were calculated for the 20 µg to 400 µg dose groups: overall total clearance ($CL/F_{,ss}$) was moderate with about 2170 mL/min with a moderate interindividual variability (43.9 gCV). The overall volume of distribution during the terminal phase ($V_z/F_{,ss}$) was high (35600 L, with 78.2% gCV). The terminal half life was about 189 h. However, based on the time of 14 days required to reach steady state and an accumulation ratio of 2.2 to 3.3, the dominant half-life of BEA 2180 is in the range of 2 to 4 days. Renal clearance of the drug was about 243 mL/min (33.9% gCV) after single dose and 284 mL/min (20.8% gCV) at steady state and exceeded the glomerular filtration rate (GFR ~ 125 mL/min). Therefore, BEA 2180 was also actively secreted. About 13% of the dose were renally excreted within one dosing interval at steady state. However, less than 5% of the inhaled dose were excreted in urine within 24 hours after first drug inhalation.

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Safety results	Multiple rising inhalative doses of BEA 2180 BR were safe and well tolerated. There were no significant or serious Adverse Events observed. One event was categorized as severe (GI-infection). 81% (48/59) of subjects in all groups experienced Adverse Events (AEs); however, over a long observation period (up to eight weeks) with four weeks of daily visits (including a daily eye control). There were few subjects with dry cough directly during/after inhalation of study drug (placebo (1), 50 µg (1), 400 µg (1)) and one subject with throat irritation after inhalation of study drug (50 µg) that occurred for a short period of time. In the higher dose groups (100 µg and higher) there were a number of subjects reporting bitter taste, classified within the nervous system disorders (term: dysgeusia). There was no relevant reduction in mean salivary secretion and there were no reports of dry mouth in the BEA 2180 BR treatment groups. Nine subjects dropped out (eight because of AEs, one out of other reasons). However, only for two of these subjects these reasons for drop out were judged related (symptoms of “dry eye” termed as Sicca-Syndrome). A causal relationship to study medication cannot be excluded, however, this clinical picture is commonly regarded to be associated with seasonal/office workplace effects. Laboratory, lung function testing, vital signs, ECG were unremarkable in general. One subject in the lowest dose group with a low baseline heart rate and retrospectively known intermittent borderline/high baseline QT- values in other studies was found to be a QT- Outlier. A causal relationship to study medication is assumed to be unlikely.

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Conclusions:

Multiple rising inhalative doses of BEA 2180 from 20 µg to 400 µg administered once daily for 21 days were safe and well tolerated.

81% (48/59) of subjects in all groups (including the Placebo group) experienced Adverse Events (AEs). However, this could be explained by the long observation period (up to eight weeks) with four weeks of daily visits (including a daily eye control).

In the higher dose groups (100 µg and higher) there were a number of subjects who reported bitter taste, coded within the nervous system disorders (dysgeusia). Nine subjects dropped out (eight because of AEs, one out of other reasons) . Only for two of these subjects the reasons for drop out were judged related (symptoms of "dry eye" termed as Sicca-Syndrome). A causal relationship to study medication cannot be excluded, however, this clinical picture is also commonly regarded to be associated with seasonal/office workplace effects.

Based on evaluation of numerical changes in R_{aw}, all administered BEA 2180 doses showed effects. BEA 2180 dose groups 100 µg, 200 µg, and 400 µg are clearly separated from the other treatment groups through all time-points measured. BEA 2180 dose groups 20 µg and 50 µg are also separated from placebo on test days 1 and 21 (for test day 21 not on trough), but not at trough values.

Protection against methacholine challenge was shown for all BEA 2180 doses on day 22 and all doses are separated from placebo.

Based on visual inspection of $AUC_{0\text{-}24}$ and $AUC_{\tau,ss}$, BEA 2180 exhibits dose-linear pharmacokinetics within the dose range tested. Steady state was achieved within approximately 14 days of treatment. The accumulation factor for C_{max} ranged from 0.814 in the 400 µg dose group to 2.07 in the 20 µg dose group (37.5% to 70.3% gCV). $AUC_{\tau,ss}$ increased 2.18 to 3.25 fold after multiple dosing compared to single dose, with low to moderate interindividual variability of 24.4% to 41.5% gCV. The terminal half-life was 189 hours. However, based on the time to steady state and the accumulation factors observed for AUC, the dominant half-life of BEA 2180 that should be used for dosing recommendations is in the range of 2 - 4 days.