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:**	
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Report date: 19 December 2007	**Number:** U07-2409	**Study period (dates):** 21 SEP 2006 – 07 DEC 2006		

Title of study:	A randomised, single-blind, placebo-controlled (within dose groups) study to assess safety, tolerability and pharmacokinetics of single rising intravenous doses (2.5 µg, 7.5 µg, 25 µg, 50 µg, 100 µg, 200 µg, 350 µg, 500 µg free cation) BEA 2180 BR in healthy male volunteers with an additional arm by inhalation in one dose group (1600 µg)
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	-
Clinical phase:	I
Objectives:	Evaluation of safety, tolerability and pharmacokinetics of single rising intravenous doses of BEA 2180 BR; additional exploration of metabolism following inhalation only
Methodology:	iv part: randomised, single-blind, placebo controlled [at each dose level], single rising dose, single centre; single dose inhalation uncontrolled
No. of subjects: **planned:**	entered: 72

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actual:	enrolled: 71 Treatment BEA 2180 BR 2.5 µg intravenous: entered:6 treated:6 analysed:6 Treatment BEA 2180 BR 7.5 µg intravenous: entered:6 treated:6 analysed:6 Treatment BEA 2180 BR 25 µg intravenous: entered:5 treated:5 analysed:5 Treatment BEA 2180 BR 50 µg intravenous: entered:6 treated:6 analysed:6 Treatment BEA 2180 BR 100 µg intravenous: entered:6 treated:6 analysed:6 Treatment BEA 2180 BR 200 µg intravenous: entered:6 treated:6 analysed:6 Treatment BEA 2180 BR 350 µg intravenous: entered:6 treated:6 analysed:6 Treatment BEA 2180 BR 500 µg intravenous: entered:6 treated:6 analysed:6 Treatment placebo intravenous: entered:16 treated:16 analysed:16 Treatment BEA 2180 BR 1600 µg per inhalation: entered:8 treated:8 analysed:8
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥21 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BEA 2180 BR solution
dose:	2.5, 7.5, 25, 50, 100, 200, 350, 500 µg
mode of admin.:	Intravenous infusion
batch no.:	B061001777
Test product:	BEA 2180 BR solution
dose:	1600 µg
mode of admin.:	Inhaled with the Respimat® A5 device
batch no.:	B052000145, B052000147 (Respimat®)
Duration of treatment:	One day (single dose) for each treatment

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Reference therapy:	Placebo solution NaCl 0.9 %
dose:	-
mode of admin.:	Intravenous infusion (duration 15 min)
batch no.:	6154A121 (100 ml), 6232A162 (250ml)
Criteria for evaluation:	
Efficacy:	Pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT, MRT_{ih}, CL, CL/F, V_z, V_z/F, V_{ss}, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Safety:	Physical examination, vital signs (BP, PR), ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistics for safety, PK and PD endpoints Dose proportionality of the iv solution of BEA 2180 BR was explored using a regression model. A 95% confidence interval for the slope was computed.

SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics:

After **intravenous infusion**, BEA 2180 showed a triphasic disposition profile, with a rapid decline up to two hours and with the terminal phase starting at approximately 12 hours. Maximum plasma concentrations were generally measured at the end of the 15 min infusion period. Pharmacokinetic parameters depending on terminal half-life were most reliably determined in the highest dose group of 500 µg BEA 2180 and are given below. The terminal half-life of BEA 2180 after intravenous infusion was approximately 18 hours. Steady state volume of distribution (V_{ss}) and total clearance (CL) were high (215 L with 23.1% gCV and 1060 mL/min, 42.7% gCV, respectively). Therefore, BEA 2180 is extensively distributed throughout the body and rapidly cleared from systemic circulation. Urinary excretion accounted for approximately 30% within 72 hours after intravenous infusion. Renal clearance ($CL_{R,0-24}$) ranged from 309 mL/min to 458 mL/min (dose groups 200 to 500 µg) and exceeded the glomerular filtration rate. This supports the assumption that BEA 2180 is actively secreted into the renal tube presumably via cation transporters.

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Efficacy results (cont.):	Within the investigated dose ranges, AUC_{0-4} (25-500 µg BEA 2180) and urinary excretion (2.5- 500 µg BEA 2180) increased in proportion to the dose. AUC_{0-24} (200-500 µg BEA 2180) also appeared to increase in proportion to the dose, however, due to the paucity of available values, dose proportionality of AUC_{0-24} could not reliably be assessed. Regarding C_{max} (2.5-500 µg BEA 2180) the deviation from dose proportionality appeared to be slight and not of clinical relevance. Overall, BEA 2180 is considered to exhibit linear pharmacokinetics after intravenous infusion. As only two subjects in the intravenous part of the study were CYP 2D6 poor metabolizers, no firm conclusion regarding the influence of CYP 2D6 metabolizer status on the pharmacokinetics of BEA 1280 after intravenous infusion could be drawn. **After inhalation** maximum plasma concentrations of BEA 2180 were measurable about 2 minutes after end of inhalation and declined rapidly to about one tenth 2 hours thereafter. Maximum plasma concentrations of the two metabolites CD 1975 ZW and CD 1976 ZW were generally measurable 4 and 6 hours after inhalation of BEA 2180, respectively. CD 1975 ZW accounted for 2.81% (36.4% gCV) and CD 1976 ZW for 4.63% (43.2% gCV) of known drug-related material after single dose inhalation of 1600 µg BEA 2180. Therefore CD 1975 ZW and CD 1976 ZW are minor unique human metabolites with a mean exposure of less than 5% of known drug-related material in plasma. Both metabolites CD 1975 ZW and CD 1976 ZW were detectable in the seven CYP 2D6 extensive metabolizers of the inhalative part of the study, whereas neither metabolite was detected in the CYP 2D6 poor metabolizer.
Safety results:	No deaths or serious adverse events occurred in this study. Laboratory and 12-lead ECG analyses did not show clinically relevant changes. Out of 71 study subjects, 12 subjects reported 15 AEs of which 7 were judged to be drug related (with dry mouth being the most prominent in four cases). AEs were mild (10 cases) to moderate (5 cases) in intensity and resolved without intervention until the end of the study.

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Conclusions:

After intravenous infusion, BEA 2180 showed a triphasic disposition profile. The terminal half-life of BEA 2180 after intravenous infusion was approximately 18 hours. Steady state volume of distribution (V_{ss}) and total clearance (CL) were high in the 500 µg dose group (215 L with 23.1% gCV and 1060 mL/min, 42.7% gCV, respectively). Overall, BEA 2180 is considered to exhibit linear pharmacokinetics after intravenous infusion.

After single dose inhalation of 1600 µg BEA 2180 BR, CD 1975 ZW accounted for 2.81% and CD 1976 ZW for 4.63% of known drug-related material in plasma. Consequently, CD 1975 ZW and CD 1976 ZW are minor unique human metabolites with a mean exposure of less than 5% of known drug-related material in plasma.

BEA 2180 BR, an antimuscarinic compound, was safe and well tolerated in a single dose up to 500µg i.v. or 1600 µg per inhalation based on physical examination, close 12-lead ECG ECG monitoring during the saturation and elimination phase, laboratory analysis and solicited adverse event reporting. AEs were observed within the expected profile and intensity. Being a CYP2D6 metabolizer did not change the tolerability.

From the results of this study, no concerns can be raised to use BEA 2180 in the studied dose range and way of application in future studies. This includes the use of infused radio-labelled BEA 2180 in future pharmacokinetic studies.