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: Not applicable			
Name of active ingredient: BEA 2180 BR		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 23 JUN 2009	**Trial No. / U No.:** 1205.18 / U09-3423-01	**Date of trial:** 29 APR 2008 – 27 OCT 2008	**Date of revision** (if applicable)**:** Not applicable

Title of trial:	A randomised, double-blind, placebo-controlled (within dose groups) study to evaluate safety, tolerability and pharmacokinetics of multiple rising inhalative doses (50 µg, 100 µg and 200 µg q.d. for 14 days) of BEA 2180 BR in Japanese healthy male volunteers
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted] Japan
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	To evaluate the safety and tolerability of BEA 2180 BR in healthy Japanese male volunteers after oral inhalation of repeated rising doses of 50 µg, 100 µg, and 200 µg (free cation) for 14 days in comparison with placebo
Methodology:	Randomised, double-blind and placebo-controlled within a dose group, multiple-rising-dose trial
No. of subjects:	
planned:	to be entered: 36 subjects
actual:	enrolled: 48 subjects, entered: 36 subjects Treatment with BEA 2180 BR 50 µg: entered: 9, treated: 9, analysed (for primary endpoint): 9 Treatment with BEA 2180 BR 100 µg: entered: 9, treated: 9, analysed (for primary endpoint): 9 Treatment with BEA 2180 BR 200 µg: entered: 9, treated: 9, analysed (for primary endpoint): 9 Treatment with placebo: entered: 9, treated: 9, analysed (for primary endpoint): 9
Diagnosis and main criteria for inclusion:	Healthy Japanese male volunteers; age: ≥20 and ≤35 years; body mass index range: ≥18.5 and ≤25.0 kg/m^2

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable			
Name of active ingredient: BEA 2180 BR		**Page:** 2 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 23 JUN 2009	**Trial No. / U No.:** 1205.18 / U09-3423-01	**Date of trial:** 29 APR 2008 – 27 OCT 2008	**Date of revision** (if applicable)**:** Not applicable

Test product:	BEA 2180 BR solution
dose:	50 µg, 100 µg, and 200 µg once daily
mode of admin.:	Oral inhalation via the Respimat® inhaler A5
batch no.:	B062000697 for BEA 2180 BR Respimat® solution (25 µg/actuation), B06200704 for BEA 2180 BR Respimat® solution (50 µg/actuation), and B062000705 for BEA 2180 BR Respimat® solution (100 µg/actuation)
Reference therapy:	Placebo solution
dose:	Not applicable
mode of admin.:	Oral inhalation via the Respimat® inhaler A5
batch no.:	B062000699 (including placebo used for training)
Duration of treatment:	14 days
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Pharmacokinetic parameters: After the first dose: C_{max}, t_{max}, $AUC_{\tau,1}$, AUC_{0-tz}, $Ae_{\tau,1}$, $fe_{\tau,1}$, $CL_{R,t1-t2}$ After the last dose: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $C_{pre,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{ih,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$, $Ae_{\tau,ss}$, $fe_{\tau,ss}$, $CL_{R,t1-t2,ss}$ Accumulation ratios: $R_{A,Cmax}$, $R_{A,AUC}$, $R_{A,Ae}$ Attainment of steady state, dose proportionality of pharmacokinetics
Safety:	Physical examination, vital signs (blood pressure and pulse rate), 12-lead electrocardiography (ECG), clinical laboratory tests, adverse events, and tolerability
Statistical methods:	Safety and pharmacokinetic parameters were summarised by using descriptive statistics. Dose proportionality was explored by using the power model for the relationship between the dose and pharmacokinetic endpoints. Attainment of steady state was explored by using repeated measures analysis of variance.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable			
Name of active ingredient: BEA 2180 BR		**Page:** 3 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 23 JUN 2009	**Trial No. / U No.:** 1205.18 / U09-3423-01	**Date of trial:** 29 APR 2008 – 27 OCT 2008	**Date of revision** (if applicable)**:** Not applicable

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

- After multiple inhaled administration of BEA 2180 BR (Day 14), the plasma concentrations of BEA 2180 reached a peak at around 0.083 to 0.250 hour (5 to 15 min). The plasma concentrations rapidly declined within 4 hours, and then slightly increased between 8 hours and 12 hours after inhalation. From 24 hours after multiple inhaled administration, plasma concentrations declined gradually in the terminal phase. The terminal half-lives at the steady state were 104 to 157 hours. The cumulative fractions of BEA 2180 excreted in the urine were approximately 13% to 18% of the dose within the dosing interval of 0 to 24 hours at steady state. C_{max} did not show relevant accumulation with multiple administration, and $R_{A,AUC0-24}$ was 2.18 to 3.40. The results of visual inspection and statistical analysis indicated that $C_{max,ss}$, AUC_{0-24}, and $AUC_{0-24,ss}$ of BEA 2180 increased dose-proportionally within the dose range investigated.
- CD 1975 ZW, a metabolite, was not detected in plasma from the most of the subjects, precluding any conclusion as to the pharmacokinetics related to plasma concentration of CD 1975 ZW in this trial. Cumulative fraction of CD 1975 ZW excreted in the urine was 0.266% of the dose within the dosing interval of 0 to 24 hours at steady state in the BEA 2180 BR 200 µg group.
- The plasma concentrations of CD 1976 ZW, a metabolite, were at almost the same level from before the last inhaled administration to 48 hours after the last inhaled administration. Cumulative fractions of CD 1976 ZW excreted in the urine were approximately 0.5% to 0.6% of the dose within the dosing interval of 0 to 24 hours at steady state. The results of visual inspection and statistical analysis indicated that $C_{max,ss}$ and $AUC_{0-24,ss}$ of CD 1976 ZW increased less than proportionally within the dose range investigated.
- The metabolic ratios of CD 1975 ZW based on $Ae_{0-24,ss}$ was less than 0.02. The metabolic ratios of CD 1976 ZW based on $AUC_{0-24,ss}$ were 0.115 to 0.119. The metabolic ratios of CD 1976 ZW based on $C_{max,ss}$ and $Ae_{0-24,ss}$ were less than 0.05.
- BEA 2180 and CD 1976 ZW were considered to have reached the steady state before the administration on Day 10 and Day 12 at the latest, respectively.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable			
Name of active ingredient: BEA 2180 BR		**Page:** 4 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 23 JUN 2009	**Trial No. / U No.:** 1205.18 / U09-3423-01	**Date of trial:** 29 APR 2008 – 27 OCT 2008	**Date of revision** (if applicable)**:** Not applicable

Safety results:

No death, other serious adverse events, nor other significant adverse events were reported in this trial.
Of the 27 subjects treated with BEA 2180 BR, 2 (7.4%) reported 1 adverse event each: gingivitis and stomatitis; both events were mild. Neither of the adverse events was considered to be related to the investigational product by the investigator.
Clinically relevant changes from the baseline values were not noted in laboratory test results, vital signs (systolic or diastolic blood pressure or pulse rate), nor ECGs.
Global tolerability was good in all the subjects.

Conclusions:

The plasma concentrations of BEA 2180 rapidly reached a peak at around 0.083 to 0.250 hour (5 to 15 min) after multiple drug inhalation. The terminal half-lives at steady state were 104 to 157 hours. The cumulative fractions of BEA 2180 excreted in the urine were approximately 13% to 18% of the dose within the dosing interval of 0 to 24 hours at steady state. C_{max} did not show relevant accumulation during multiple administration, and $AUC_{0-24,ss}$ increased approximately 2- to 3-fold compared with AUC_{0-24}. $C_{max,ss}$, AUC_{0-24}, and $AUC_{0-24,ss}$ of BEA 2180 increased dose-proportionally within the dose range investigated. The metabolic ratio of CD 1975 ZW based on $Ae_{0-24,ss}$ was less than 0.02. The metabolic ratios of CD 1976 ZW based on $AUC_{0-24,ss}$ were approximately 0.12. BEA 2180 and CD 1976 ZW were considered to have reached the steady state before the administration on Day 10 and Day 12 at the latest, respectively. The exposures in Japanese were comparable to those in non-Japanese.
BEA 2180 BR 50, 100, and 200 μg were safe and well tolerated in the healthy Japanese male volunteers.