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: 15 October 2007	**Number:** U07-2053	**Study period (dates):** 06 December 2006 18 January 2007		

Title of study:	A randomised, single-blind, placebo-controlled (within dose groups) study to assess safety, tolerability and pharmacokinetics of single rising peroral doses (400, 800, 1200 µg free cation) BEA 2180 BR in healthy male volunteers.
Investigator:	[redacted]
Study centre(s):	[redacted] Germany
Publication (reference):	Data on this study has not been published.
Clinical phase:	I
Objectives:	The objective of the current study was to investigate safety, tolerability and pharmacokinetics of BEA 2180 BR following peroral doses of 400µg to 1200 µg in healthy male volunteers.
Methodology:	Randomised, single-blind, placebo-controlled (at each dose level), single rising dose, single centre
No. of subjects: **Total** **each treatment** **planned:** **actual:**	24 8 per dose group (6 on drug and 2 on placebo) entered: 24 enrolled: 24 Treatment BEA 2180 BR: entered: 18 treated: 18 analysed (for pharmacokinetics): 18 Treatment Placebo: entered: 6 treated: 6 analysed (for pharmacokinetics): 0
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age: ≥21 and ≤55 years, BMI: ≥18.5 and ≤30.0 kg/m^2
Test product: **dose:** **mode of admin.:** **batch no.:**	BEA 2180 BR solution 400 µg, 800 µg, and 1200 µg (calculated as BEA 2180 BR cation nominal) Peroral solution taken with a glass of water 6BA01
Duration of treatment:	Single dose

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: -		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BEA 2180 BR		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 15 October 2007	**Number:** U07-2053	**Study period (dates):** 06 December 2006 18 January 2007		

Reference therapy:	tartaric acid 0.1% as placebo
dose:	Not applicable
mode of admin.:	Peroral solution taken with a glass of water
batch no.:	B05035
Criteria for evaluation:	
Pharmacokinetics:	Secondary endpoints: C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t-t2}, CLR_{t1-t2}
Safety:	Physical examination, vital signs (blood pressure, pulse rate, respiratory rate, and oral body temperature), 12-lead electrocardiogram, clinical laboratory tests (haematology, clinical chemistry and urinalysis), adverse events, and assessment of tolerability by investigator
Statistical methods:	Descriptive statistics for safety and pharmacokinetic endpoints were calculated. Dose proportionality of BEA 2180 BR was explored using a regression model. A 95% confidence interval for the slope was computed.

SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

Plasma concentrations of BEA 2180 after single oral administration of 400, 800 and 1200 µg BEA 2180 BR were very low (<108 pg/mL) for all dose groups and all time points. Plasma concentrations after oral administration were generally measurable only up to 6 hours in the two lower dose groups and up to 9 hours in the highest dose group tested. Maximum plasma concentrations (C_{max}) of BEA 2180 after oral administration were reached between 0.50 and 4.05 hours considering all dose groups, with median t_{max} of between 1.51 and 2.01 hours.

Generally a high variability was observed in the data among all dose groups which is most likely due to the very low oral bioavailability. Two subjects in the 1200 µg dose groups exhibited considerably higher plasma concentrations. Since no genotyping was performed in this trial, the reason for the higher exposure of these two subjects remains unclear.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: -		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BEA 2180 BR		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 15 October 2007	**Number:** U07-2053	**Study period (dates):** 06 December 2006 18 January 2007		

Pharmacokinetic results continued:

Considering the short time frame with detectable plasma concentrations, it is very likely that the terminal phase is not visible. Therefore, the calculated terminal half-lives are probably underestimated, and the corresponding pharmacokinetic parameters are of limited significance.

Since the $CL_{R,0-12}$ of 278 mL/min exceeded the glomerular filtration rate (125 mL/min), BEA 2180 is also actively secreted, presumably via cation transporters in the renal tube as described for other N-quaternary drugs.

The analysis of AUC_{0-6}, C_{max} and Ae_{0-tz} using the power model provided very wide 95% confidence intervals for the slope, reflecting the high variability in all three pharmacokinetic parameters tested. Therefore, valid conclusions about dose proportionality of BEA 2180 after oral administration cannot be drawn. The high inter-individual variability in the data is most likely due to the very low oral bioavailability of BEA 2180 after oral administration.

		400 µg (N=6)		800 µg (N=6)		1200 µg (N=6)	
		gMean	gCV[%]	gMean	gCV[%]	gMean	gCV[%]
C_{max}	[pg/mL]	9.40	111	17.8	59.2	25.5	210
$C_{max,norm}$	[(pg/mL)/µg]	0.0235	111	0.0222	59.2	0.0212	210
t_{max}[1]	[h]	2.00	1.00-2.02	1.51	0.500-4.00	2.01	1.00-4.05
AUC_{0-6}[2]	[pg·h/mL]	58.6	42.9	64.5	55.6	118	214
$AUC_{0-6,norm}$[2]	[(pg·h/mL)/µg]	0.146	42.9	0.0806	55.6	0.0987	214
AUC_{0-tz}	[pg·h/mL]	24.9	249	67.1	64.0	190	431
$CL_{R,0-12}$	[mL/min]	---	---	---	---	278	18.3
Ae_{0-tz}	[ng]	888	94.6	1020	62.3	4010	199
fe_{0-tz}	[%]	0.222	94.6	0.127	62.3	0.334	199

[1]Median and range
[2]For 400 µg oral : N=4
Source data: Tables 15.5.2.1: 1-10

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: -		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BEA 2180 BR		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 15 October 2007	**Number:** U07-2053	**Study period (dates):** 06 December 2006 18 January 2007		

Safety results:	In 4 of the 18 subjects treated with BEA 2180 BR and in 3 of the 6 subjects treated with placebo, mild to moderate adverse events (headache, fatigue, AST/ALT increased, vomiting, nausea) were observed. All events were resolved at the end of the study without sequelae. No deaths, no serious and no significant adverse events were observed. No relevant influence on safety parameters, i.e., vital signs including respiratory rate, ECG parameters, or safety laboratory parameters, was observed. Overall tolerability was assessed to be good in all subjects.
Conclusions:	After single oral administration of 400, 800 and 1200 µg BEA 2180 BR plasma concentrations of BEA 2180 were very low for all dose groups and all time points and generally measurable only up to 6-9 hours after drug administration. These data suggest a low oral bioavailability of BEA 2180 as expected for an N-quaternary drug. Considering the short time frame with detectable plasma concentrations, it is very likely that the terminal phase is not visible. Therefore, the calculated terminal half-lives are probably underestimated, and the corresponding pharmacokinetic parameters are of limited significance. The geometric mean cumulative fraction of BEA 2180 excreted in urine (% of dose) was very low with about 0.3%. The $CL_{R,0-12}$ obtained in the highest dose group of 1200 µg, of 278 mL/min (gCV 18.3%), exceeded the glomerular filtration rate and suggests that BEA 2180 is also actively secreted, presumably via cation transporters in the renal tube. Due to the high inter-individual variability in the data, valid conclusions about dose proportionality of BEA 2180 after oral administration cannot be drawn. The results of this study show that single oral doses of 400, 800, and 1200 µg BEA 2180 BR are safe and well tolerated in healthy male subjects compared to placebo. No relevant influence on safety laboratory parameters, vital signs including respiratory rate or ECG parameters was observed.