Clinical Study Synopsis for Public Disclosure

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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		**EudraCT No.:** 2006-004125-28	
Name of active ingredient: BEA 2180 BR		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 21 JUL 2008	**Trial No. / U No.:** 1205.8 / U08-1765-01	**Dates of trial:** 28 MAR 2007 – 21 MAY 2007	**Date of revision** (if applicable)**:**

Title of trial:	Investigation of the metabolism and pharmacokinetics of 1200 µg (free cation) [^{14}C] BEA 2180 BR administered orally compared to 500 µg (free cation) [^{14}C] BEA 2180 BR administered intravenously in healthy male volunteers in an open label, single-dose and parallel study design
Principal Investigator:	[redacted]
Trial site:	[redacted] The Netherlands
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The primary objectives were to determine the basic pharmacokinetics of BEA 2180 BR, its metabolites CD 1975 ZW and CD 1976 ZW, and [^{14}C] radioactivity including excretion mass balance, excretion pathways and metabolism following oral (p.o.) and intravenous (i.v.) administration of [^{14}C] BEA 2180 BR. The secondary objectives were to determine safety and tolerability following single dose oral and i.v. administration of BEA 2180 BR in healthy male volunteers.
Methodology:	Open-label, single dose, parallel group design in healthy male volunteers with an in-house part for at least 10 days
No. of subjects:	
planned:	entered: 14
actual:	enrolled: 14 Treatment 1: 1200 µg oral solution entered: 6 treated: 6 analysed (for primary endpoint): 6 Treatment 2: 500 µg i.v. as 15 min infusion entered: 8 treated: 8 analysed (for primary endpoint): 8

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 35 to 70 years, body mass index 18.5 to 29.9 kg/m^2 Screening for cytochrome P450 2D6 (CYP 2D6) metaboliser status was performed under a separate protocol prior to screening for this study.
Test product:	BEA 2180 BR as oral solution
dose:	1200 µg (calculated as cation) (2.25 MBq)
mode of admin.:	By mouth
batch no.:	050181/24mLBEA2180/15Apr07
Reference therapy:	BEA 2180 BR as solution for infusion to be reconstituted with isotonic saline
dose:	500 µg (calculated as cation) (1.6 MBq)
mode of admin.:	Intravenous infusion for 15 min
batch no.:	050181/15mLBEA2180/22Apr07
Duration of treatment:	One day (single dose) for each treatment
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Pharmacokinetics (PK): Individual concentration-time profiles of [^{14}C] radioactivity in whole blood, plasma, urine and faeces Individual concentration-time profiles of BEA 2180 BR and its metabolites CD 1975 ZW and CD 1976 ZW in plasma and urine Rate and extent of excretion and mass balance based on the total radioactivity in urine and faeces Elucidation of metabolite structures and identification of major metabolites in urine, faeces, and plasma (if feasible) in comparison with various animal species (reported separately) $C_{blood\ cell}/C_{plasma}$ ratio of [^{14}C] radioactivity Estimation of PK parameters using non-compartmental methods from the plasma and urine concentrations of BEA 2180 BR and its metabolites CD 1975 ZW and CD 1976 ZW and [^{14}C] radioactivity in whole blood, plasma and urine

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Safety:	Tolerability, adverse events (AEs), physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), and clinical laboratory tests
Statistical methods:	Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Pharmacokinetics after oral administration

The maximum plasma concentration (C_{max}) of [^{14}C] radioactivity was 1210 pmoleq/L (30.2% gCV), which exceeded the C_{max} of BEA 2180 (94.0 pmol/L (80.0% gCV), CD 1975 ZW (20.9 pmol/L (47.0% gCV) and CD 1976 ZW (37.9 pmol/L (72.0% gCV). Similarly, BEA 2180 and its metabolites CD 1975 ZW and CD 1976 ZW had only a minor contribution to total radioactivity in plasma (BEA 2180: 5.30%; CD 1975 ZW plus CD 1976 ZW: 2.11%).

Urinary excretion of drug-related radioactivity (fe_{0-tz}) was 4.59% (36.0% gCV) and thus only played a minor role in the overall elimination following oral administration. Similar to the data in plasma, the fe_{0-tz} of BEA 2180 (0.505%, 139% gCV), CD 1975 ZW (0.0437%, 136% gCV), and CD 1976 ZW (0.103%, 94.5% gCV) were lower than that of total radioactivity. BEA 2180 was actively secreted into the urine.

The absolute bioavailability of BEA 2180 was about 1.73% and the fraction absorbed (F_a) was at least 10.5%.

In summary, the major route of excretion of total [^{14}C] radioactivity after oral administration of [^{14}C] BEA 2180 BR was the faeces, as demonstrated by the cumulative fraction excreted in faeces until the last measurable time point ($fe_{faeces,0-tz}$) of 92.8%. The overall gMean recovery of [^{14}C] radioactivity in urine and faeces was 97.6% and can be considered almost complete.

Pharmacokinetics after intravenous administration

CYP 2D6 extensive metabolisers

The C_{max} of [^{14}C] radioactivity was 64600 pmoleq/L (17.5% gCV), which exceeded the C_{max} of BEA 2180 (59000 pmol/L, 19.0% gCV), CD 1975 ZW (37.8 pmol/L, 76.5% gCV), and CD 1976 ZW (60.8 pmol/L, 65.6% gCV). The

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contribution of BEA 2180 to total radioactivity in plasma was 32.1%. CD 1975 ZW and CD 1976 ZW together contributed about 1.20%. BEA 2180 did not distribute into red blood cells.

For [^{14}C] radioactivity in plasma, the total clearance (CL) was 319 mL/min (23.2% gCV), the terminal half-life ($t_{1/2}$) was 18.7 h (64.4% gCV), and the volume of distribution at steady state (V_{ss}) was 250 L (61.8% gCV). For BEA 2180, the CL was 995 mL/min (15.4% gCV), the $t_{1/2}$ was 12.7 h (44.7% gCV), and the V_{ss} was high (146 L, 74.7% gCV).

Urinary excretion of drug related radioactivity (fe_{0-tz}) was 53.9% (7.78% gCV) of the BEA 2180 BR dose, whereas excretion of BEA 2180 accounted for 33.3% (9.70% gCV) of the BEA 2180 BR dose. The contributions of CD 1975 ZW and CD 1976 ZW to urinary excretion were minor (CD 1975 ZW: 0.264%, 91.0% gCV; CD 1976 ZW: 0.447%, 47.7% gCV. Renal clearance (CL_R) of BEA 2180 (326 mL, 21.6% gCV) exceeded the glomerular filtration rate, suggesting that BEA 2180 was actively secreted into the urine.

CYP 2D6 poor metabolisers

Concentrations of CD 1975 ZW and CD 1976 ZW could not be detected in the plasma and urine of the two CYP 2D6 poor metabolisers. The plasma concentration-time profiles of [^{14}C] radioactivity and parent compound were almost identical. BEA 2180 contributed 84.8% and 96.1% of total radioactivity in plasma.

The C_{max} of BEA 2180 in CYP 2D6 poor metabolisers was comparable to that in extensive metabolisers, but plasma concentrations of BEA 2180 declined more slowly than in CYP 2D6 extensive metabolisers. This observation was confirmed by reductions in CL of BEA 2180 of 43.3% and 34.1% and increases in $t_{1/2}$ of a factor of 2.1 and 3 in the two CYP 2D6 poor metabolisers compared with extensive metabolisers. Consequently, the $AUC_{0-\infty}$ of BEA 2180 increased by a factor of 1.75 and 1.51 in CYP 2D6 poor metabolisers. The CL of [^{14}C] radioactivity in plasma was 1.5 and 2 times higher in poor metabolisers than in extensive metabolisers.

Similar to the result in plasma, the fe_{0-tz} of BEA 2180 was higher in CYP 2D6 poor metabolisers than in CYP 2D6 extensive metabolisers and the fraction of the dose excreted as parent compound was similar to that of [^{14}C] radioactivity.

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	The CL_R of BEA 2180 in CYP 2D6 poor metabolisers was comparable to that of CYP 2D6 extensive metabolisers. Mass balance In CYP 2D6 extensive metabolisers, 53.9% of total [^{14}C] radioactivity was excreted in the urine and 41.6% was excreted in the faeces; the elimination of total [^{14}C] radioactivity in CYP 2D6 poor metabolisers was comparable. The overall gMean recovery of [^{14}C] radioactivity in urine and faeces was 95.8% and can be considered almost complete. The Asian subject in the 500 µg i.v. group displayed pharmacokinetic characteristics similar to those of the white subjects with respect to concentrations of BEA 2180, CD 1975 ZW, and CD 1976 ZW in plasma and urine and [^{14}C] radioactivity in plasma, whole blood and urine and faeces.
Safety results:	Eleven of 14 subjects experienced AEs during the trial. All AEs were mild in intensity. The most frequently reported AE was dry mouth. In the 1200 µg p.o. group, three of six subjects experienced AEs, including one subject who experienced nausea which the investigator considered possibly drug-related. In the 500 µg i.v. group, all eight subjects experienced AEs; four subjects experienced dry mouth which was considered possibly drug-related and one subject, who was a CYP 2D6 poor metaboliser, also experienced somnolence which was considered possibly drug-related. No deaths and no serious AEs occurred. No findings of clinical laboratory parameters, vital signs, or ECG were considered clinically relevant. Tolerability was assessed as 'good' in all subjects.
Conclusions:	After oral administration of 1200 µg BEA 2180 BR, the absolute bioavailability of BEA 2180 was about 1.73% and the fraction absorbed (F_a) was at least 10.5%. The overall gMean recovery of [^{14}C] radioactivity was 97.6%; 92.8% was excreted in the faeces and 4.59% in the urine. In plasma, BEA 2180 contributed 5.30% of total radioactivity and CD 1975 ZW and CD 1976 ZW together contributed 2.11%; therefore, CD 1975 ZW and CD 1976 ZW are minor unique human metabolites after oral administration. It was concluded that one or more additional metabolites were formed after oral administration in CYP 2D6 extensive metabolisers. The metabolic pattern of additional metabolites is under further investigation and will be reported separately. After intravenous administration of 500 µg BEA 2180 BR, the overall gMean

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recovery of [^{14}C] radioactivity was 95.8%. In CYP 2D6 extensive metabolisers, 53.9% of [^{14}C] radioactivity was eliminated in the urine and 41.6% in the faeces. Elimination of total [^{14}C] radioactivity in CYP 2D6 poor metabolisers was comparable. In CYP 2D6 extensive metabolisers, the contribution of BEA 2180 to total radioactivity in plasma was 32.1%. CD 1975 ZW and CD 1976 ZW together contributed about 1.20% of total radioactivity in plasma; therefore, these are minor unique human metabolites after intravenous administration. It was concluded that one or more additional metabolites were formed after intravenous administration in CYP 2D6 extensive metabolisers. In CYP 2D6 poor metabolisers, total radioactivity in plasma was mostly related to BEA 2180 (84.8% and 96.1%).

Single doses of [^{14}C] BEA 2180 BR were safe and well tolerated in healthy male volunteers. The results of this study do not indicate any safety concerns for future trials of BEA 2180 BR.