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.

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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.

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Report date: 09 August 2007	**Number:** U07-1759	**Study period (dates):** 04 JULY 06 - 22 AUG 06		

Title of study:	Metabolism and pharmacokinetics of [^{14}C]-BIBW 2992 MA2 after administration of single doses of 15 mg [^{14}C]-BIBW 2992 MA2 oral solution in healthy male volunteers
Investigator:	[redacted]
Study center(s):	[redacted] Netherlands
Publication (reference):	Data from this study have not been published.
Clinical phase:	I
Objectives:	The aim of the study was to investigate the metabolism and pharmacokinetics of BIBW 2992 MA2 after a single oral dose of [^{14}C]-radiolabelled BIBW 2992 MA2 in healthy male volunteers. Metabolites in human plasma and excretions were measured, the structures of the metabolites analysed and compared with metabolites in animals. In addition, the mass-balance of excretion, the protein binding of [^{14}C]-radioactivity, the plasma concentrations of BIBW 2992 MA2, and the [^{14}C]-radioactivity in blood cells, plasma, urine and faeces were measured. The safety and tolerability of BIBW 2992 were also investigated.
Methodology:	Open, single dose, metabolic profiling and pharmacokinetic study in healthy male subjects receiving oral [^{14}C]-BIBW 2992 MA2
No. of subjects:	
planned:	Entered: 8
actual:	Enrolled: 8 Single treatment Entered: 8 treated: 8 analysed (for primary endpoint): 8
Diagnosis and main criteria for inclusion:	Healthy male subjects from 35 to 60 years of age with a body mass index ranging from 18.5 to 29.9 kg/m^2
Test product:	[^{14}C]-BIBW 2992 MA2 oral solution
dose:	15 mg, single dose
mode of admin.:	Oral
batch no.:	B061001332
Duration of treatment:	1 day

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Reference therapy:	No reference treatment
dose:	Not applicable
mode of admin.:	Not applicable
batch no.:	Not applicable
Criteria for evaluation:	
Efficacy:	Pharmacokinetics: [^{14}C]-radioactivity concentrations were measured in plasma, whole blood, faeces, and urine. Pharmacokinetic parameters were determined from radioactivity concentrations in whole blood and plasma. The rate and extent (mass balance) of BIBW 2992 MA2 excretion were determined from plasma, urine and faeces radioactivity. Plasma protein binding of [^{14}C]-radioactivity to proteins was measured. BIBW 2992 MA2 concentrations in plasma and urine were measured. The pharmacokinetic parameters of BIBW 2992 MA2 were calculated from plasma and urine concentrations.
Safety:	Pulse rate (PR), systolic and diastolic blood pressure (BP), 12-lead electrocardiograms (ECG), routine laboratory measurements, adverse events (AEs), tolerability
Statistical methods:	Descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetic results:

The contribution of renal excretion to the total body clearance of BIBW 2992 related [^{14}C]-radioactivity was low. The renal clearance for BIBW 2992 and also for [^{14}C]-radioactivity in plasma was low. The major route of elimination of total [^{14}C]-radioactivity was found to be via faeces. The overall recovery of [^{14}C]-radioactivity was 89.5%, and can therefore be regarded as almost complete mass balance.

For BIBW 2992 as well as for [^{14}C]-plasma and whole blood radioactivity, maximum plasma concentrations were reached around 6 h after dosing.

The shapes of the BIBW 2992 plasma, [^{14}C]-plasma and [^{14}C]-whole blood radioactivity concentration-time profiles were comparable for up to 12 h after dosing. Afterwards, BIBW 2992 plasma concentrations declined more rapidly compared to the [^{14}C]-plasma and [^{14}C]-whole blood radioactivity concentrations. Due to differences in the lower limit of quantification (LLQ) ranges of the bioanalytical assays for BIBW 2992 in plasma, for [^{14}C]-radioactivity in plasma and for [^{14}C]-radioactivity in whole blood, there were differences in the absorption phases of BIBW 2992 compared to [^{14}C]-radioactivity.

The comparison of gMean total exposure ($AUC_{0-\infty}$ values) of BIBW 2992 in plasma (163 ng·h/mL), of [^{14}C]-radioactivity in plasma (769 ngeq·h/mL) as well as in whole blood (1770 ngeq·h/mL) indicated that the $AUC_{0-\infty}$ of BIBW 2992 only corresponded to 23% of the total exposure of [^{14}C]-radioactivity in plasma. In comparison to the AUC_{0-24} values, this indicated that at later time points (>24 h after dosing) most of the [^{14}C]-radioactivity in plasma was in the form of BIBW 2992 metabolite(s) and not BIBW 2992 itself. Also, the ratio of the gMean $AUC_{0-\infty}$ value of [^{14}C]-radioactivity in plasma to whole blood (43%) indicated that at later time points (>24 h after dosing), most of the [^{14}C]-radioactivity was related to BIBW 2992 metabolite(s) in whole blood or due to BIBW 2992 itself bound to whole blood components. However, this should be considered with some caution and should be regarded only as qualitative result, since the $\%AUC_{tz-\infty}$ for [^{14}C]-radioactivity in plasma was 64% and for [^{14}C]-radioactivity in whole blood 70.6%.

The gMean terminal half-life ($t_{1/2}$) was 33.9 h for BIBW 2992, 118 h for [^{14}C]-radioactivity in plasma and 195 h for [^{14}C]-radioactivity in whole blood indicating the presence of one or more metabolite(s) of BIBW 2992 in plasma and in whole blood with a longer terminal half-life than BIBW 2992.

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	The main metabolite of BIBW 2992 in plasma and in whole blood may be to a large extent covalently bound BIBW 2992 to either plasma proteins or whole blood components. Therefore, the terminal half life of [^{14}C]-radioactivity in plasma should be in the range of the half –life of human serum albumin which is in the range of 12 to 20 days. The terminal half life of [^{14}C]-radioactivity in whole blood should be in the range of the half -life of human red blood cells which is in the range of 60 to 120 days. Thus, the terminal half-life for [^{14}C]-radioactivity in plasma and in whole blood might have been underestimated in this trial. The terminal half-life of BIBW 2992 determined in healthy male subjects was comparable to the ones found for BIBW 2992 in cancer patients [U06-2055-01, U07-3025]. A relatively high apparent total body clearance (CL/F) for BIBW 2992 was determined (1530 mL/min). The gMean CL/F value for the [^{14}C]-radioactivity in plasma and whole blood was low (325 mL/min and 141 mL/min, respectively). BIBW 2992 exhibited a high apparent volume of distribution (V_z/F) during the terminal phase, which might indicate high tissue distribution of the drug. The gMean V_z/F value for BIBW 2992 were around 4500 L, for the [^{14}C]-radioactivity in plasma around 3330 L and for [^{14}C]-radioactivity in whole blood around 2390 L. This indicated that the metabolite(s) of BIBW 2992 in plasma and in whole blood have a lower volume of distribution than BIBW 2992 itself. The apparent values obtained for total body clearance and volume of distribution should be treated with caution as the absolute bioavailability (F) of BIBW 2992 in humans is unknown. There was moderate distribution of [^{14}C]-radioactivity into red blood cells 6 h after drug administration. The protein binding of [^{14}C]-radioactivity was between 57.2% and 88.4% at 6 h after dosing. However, the results were all in the low range of the validated range and therefore have to be treated with caution. The Asian subject participating in this trial displayed similar pharmacokinetic characteristics with respect to [^{14}C]-radioactivity in plasma, whole blood, faeces and urine as well as BIBW 2992 concentrations in plasma and in urine compared with the Caucasian subjects.
Safety results:	All 8 subjects completed the study as planned. No SAEs occurred during the study. Seven of the 8 subjects experienced at least one AE on treatment with study drug. All AEs were of CTCAE Grade 1.

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Safety results:	A variety of AEs were reported; the most frequent AEs were pollakiuria and gastrointestinal symptoms of various sorts such as abdominal distension and flatulence. The majority of subjects were reported to have recovered from the AE apart from 1 subject with pollakiuria and 1 subject with somnolence; follow-up of these two AEs was considered sufficient by the investigator. Adverse events resolved without specific treatment. Two cases of bloating, 1 of abdominal discomfort, 1 of tiredness, 1 of sleepiness and 1 of increased stool frequency were considered drug-related by the investigator. No clinically relevant changes in laboratory parameters, vitals signs, or ECGs were observed. The overall tolerability of BIBW 2992 MA2 was good.
Conclusions:	The major route of elimination of total [^{14}C]-radioactivity was found to be via faeces. The overall recovery of [^{14}C]-radioactivity was 89.5%. For BIBW 2992 as well as for [^{14}C]-plasma and whole blood radioactivity, maximum plasma concentrations were reached around 6 h after dosing. The gMean terminal half-life ($t_{1/2}$) was 33.9 h for BIBW 2992, 118 h for [^{14}C]-radioactivity in plasma and 195 h for [^{14}C]-radioactivity in whole blood indicating the presence of one or more metabolites of BIBW 2992 in plasma and in whole blood with a longer terminal half-life than BIBW 2992. A relatively high apparent total body clearance (CL/F) for BIBW 2992 was determined. The gMean CL/F values for the [^{14}C]-radioactivity in plasma and whole blood were low. BIBW 2992 as well as [^{14}C]-radioactivity in plasma and in whole blood exhibited a high apparent volume of distribution (V_z/F) during the terminal phase, which might indicate high tissue distribution of the drug. The apparent values obtained for total body clearance and volume of distribution should be treated with caution, as the absolute bioavailability (F) of BIBW 2992 in humans is unknown. There was moderate distribution of [^{14}C]-radioactivity into red blood cells. The protein binding of [^{14}C]-radioactivity was between 57.2 and 88.4% at 6 h after dosing. However, the results were all in the low range of the validated range and therefore have to be treated with caution. BIBW 2992 MA2 was safe at a single dose of 15 mg. The overall tolerability of BIBW 2992 MA2 was good.