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 Study Report**		
Name of finished product:				
Name of active ingredient: BI 14332 CL		**Page:**	**Number:**	
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Report date: 15 FEB 2007	**Number:** U07-1158	**Study period (dates):** 03 FEB 2006 to 04 APR 2006		

Title of study:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses (0.5 mg to 200 mg) of BI 14332 CL as powder in the bottle reconstituted with 0.1% tartaric acid administered to healthy male subjects. A randomised and placebo-controlled trial, double blinded within dose groups.
Investigator:	[redacted]
Study center:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	To investigate safety, tolerability and pharmacokinetics, and pharmacodynamics of BI 14332 CL
Methodology:	Randomised, placebo controlled, double-blind within dose groups, single rising dose, single trial site
No. of subjects:	
planned:	entered: 56
actual:	enrolled: 53
	BI 14332 CL: 39 0.5 mg: treated and analysed (for primary endpoint): 6 1.5 mg: treated and analysed (for primary endpoint): 5 5 mg: treated and analysed (for primary endpoint): 6 15 mg: treated and analysed (for primary endpoint): 6 50 mg: treated and analysed (for primary endpoint): 6 100 mg: treated and analysed (for primary endpoint): 5 200 mg: treated and analysed (for primary endpoint): 5 Placebo: treated and analysed (for primary endpoint): 14
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥18 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 14332 CL as powder in the bottle (PIB) reconstituted with 0.1% tartaric acid
dose:	0.5 mg, 1.5 mg, 5 mg, 15 mg, 50 mg, 100 mg and 200 mg
mode of admin.:	po taken fasted with 240 mL mineral water

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batch no.:	B051001206 for BI 14332 CL 200 mg B051001204 for BI 14332 CL 40 mg
Duration of treatment:	single dose administration
Reference therapy:	Placebo as PIB reconstituted with 0.1% tartaric acid
dose:	--
mode of admin.:	po taken fasted with 240 mL mineral water
batch no.:	B051001234
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_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$ Pharmacodynamic parameter: DPP-IV activity
Safety:	Physical examination, vital signs (BP, HR), 12-lead ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistics for safety, PK and PD endpoints were calculated.
SUMMARY – CONCLUSIONS:	
Efficacy results:	<u>Pharmacokinetics</u> A rapid rise in the plasma concentration of BI 14332 was observed after administration of single oral doses of 0.5 to 200 mg. A number of subjects showed a double peak absorption profile. C_{max} of BI 14332 increased less than proportionally between 0.5 to 15 mg and more than proportionally between 15 to 200 mg. t_{max} was highly variable in the 0.5 mg dose group (0.73 to 6 hr, CV 103%), and in the 1.5 mg dose group (1.05 to 24 hr, CV 144%). Geometric mean C_{max} ranged from 1.35 nmol/L (36.8% gCV) in the 0.5 mg dose group, to 1220 nmol/L (37.5% gCV) in the 200 mg dose group. Geometric mean $t_{1/2}$ ranged from 39.5 to 59.8 hours (geometric mean CV 22.6% and 72.4%, respectively) in the 0.5 mg dose and 1.5 mg dose group, respectively. In dose groups 5 through 100 mg, $t_{1/2}$ ranged from 81.2 hours (15 mg) to 88.2 hours (5 mg) with a low maximum geometric CV of 22.3% and increased to 111 hours in the 200 mg dose group (geometric CV of 22.9%). The geometric mean clearance CL/F ranged from 286 to 946 mL/min with a low variability (maximum gCV of 37.4%), except for the 1.5 mg dose group (gCV of 93.5%).

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Efficacy results (cont.):

Geometric mean volume of distribution V_z/F was high and generally increased with increasing doses. Mean residence time increased from 56.7 h to 103 h in the 0.5 to 5 mg dose groups and remained unchanged between the 5 and 15 mg dose groups. A steady decline was noted in higher dose groups. Renal clearance of BI 14332 was nonlinear and increased steadily with increasing plasma concentrations from 3.01% for the 1.5 mg dose to 32.2% for the 200 mg dose.

Pharmacodynamics

All of the administered doses of BI 14332 reduced plasma DPP-IV activity. Following administration of 0.5 mg BI 14332, DPP-IV activity was reduced to approximately 81%, whereas doses of 50 mg and higher reduced DPP-IV activity to approximately 5% relative to baseline activity. The median time to achieve the maximum reduction of activity increased from 1 hour in the 0.5 mg dose group to 3 hours in the 1.5 mg dose group, and decreased again to 0.5 hours in the 200 mg dose group. After 192 hours post-drug dosing, plasma DPP-IV activity had not returned to baseline levels, except for the 0.5 and 1.5 mg dose groups.

The pharmacodynamic effect was directly linked to the plasma drug concentration with no evidence for hysteresis. Concentrations above 10 nmol/L almost completely inhibited plasma DPP-IV activity. Based on this correlation, BI 14332 plasma concentrations of approximately 3 and 6 nmol/L achieved a reduction in the plasma DPP-IV activity of 50% and 80%, respectively

Safety results:

In total 14 subjects (14/53, 26.4%) reported 16 adverse events; and two subjects experienced two adverse events each. Adverse events were experienced by two subjects during the screening period, by two subjects exposed to placebo (14.3%), and by 10 subjects (25.6%) treated with BI 14332. The most frequently reported AEs by preferred term were headache (9.4%), and influenza-like illness (3.8%). The incidence of headache was lower in subjects exposed to placebo (1/14 subjects, 7.1%) compared with subjects treated with BI 14332 (4/39 subjects, 14.3%). The majority of AEs were mild in intensity; one AE was considered moderate (headache), and three AEs were considered severe (otitis media, influenza-like illness, and tension headache). Only two adverse events (dizziness and headache) were considered possibly drug related by the investigator. There were no serious adverse events and no deaths. One subject was withdrawn from the study prematurely during the post-treatment period for safety reasons due to an adverse event (otitis media) which needed treatment with antibiotics.

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Safety results (cont.):

No clinically relevant changes in haematology, clinical chemistry and urinalysis parameters were detected. There were no clinical signs of a pseudo-allergic reaction to BI 14332.

No effect of study drug treatment on vital signs was detected. The clinical ECG interpretation was normal for most of the subjects. Abnormal findings in the ECG already present at baseline were found for 4 subjects, and for 6 subjects the finding was not present at baseline. This was either due to conduction (3.8% of subjects) or rhythm abnormalities (11.3% of subjects). No individual post-dose value above 450 ms was observed for Bazett or Fridericia-corrected QTc or population QTc. Overall, there was no indication of QTc prolongation of BI 14332 based on either the Fridericia-corrected or population-corrected QTc.

Conclusions:

All administered doses of BI 14332 reduced the plasma DPP-IV activity. BI 14332 doses of 50 mg and higher reduced the DPP-IV activity to approximately 5% of baseline values within one hour of drug administration. There was a good correlation between plasma DPP-IV activity and the BI 14332 plasma concentration. Based on visual assessment BI 14332 plasma concentrations of approximately 3 and 6 nmol/L resulted in approximately 50% and 80% inhibition of DPP-IV activity, respectively.

BI 14332 was characterised by nonlinear pharmacokinetics and showed a double peak absorption profile. C_{max} and $AUC_{0-\infty}$ values increased less than proportionally in the 0.5 - 15 mg dose groups and more than proportionally in the 15 to 200 mg dose groups. Renal clearance increased with increasing plasma concentrations. The fraction of dose excreted in urine ranged from 0% in the lowest to 32.2% in the highest dose group. Renal clearance higher than 120 mL/min (from the 50 mg dose group onwards) implies active secretion of the drug. The terminal half-life ranged between 39.5 - 111 h.

Administration of single oral doses of BI 14332 was well tolerated and safe. The overall incidence of adverse events was 25.6% in subjects treated with BI 14332 and 14.3% in subjects treated with placebo, and only two adverse events were considered to be drug related by the investigator, one in the placebo group and one in the 0.5 mg dose group. There were no serious adverse events or deaths. No discernable trends were detected in any of the laboratory parameters evaluated.