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 July 2008	**Number:** U08-1754-01	**Study period (dates):** 15 NOV 06 to 16 MAR 07		

Title of study:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses (0.5, 2.5, 10 and 20 mg q.d. for 10 days) of BI 14332 CL as tablet in female and male patients with type 2 diabetes (randomised, double-blind, placebo-controlled within the dose groups), followed by a 4-week treatment part* (randomised, double-blind, placebo-controlled) of two doses (planned 5 and 20 mg) selected on the basis of tolerability and DPP-4 inhibition in the multiple rising dose part * 4-week treatment part was not performed.
Coordinating Investigator:	[redacted]
Study centres:	[redacted] Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 14332 CL following administration of multiple rising oral doses over 10 days in patients with type 2 diabetes.
Methodology:	Randomised, double-blind, placebo-controlled (within dose group), multiple rising doses in patients with type 2 diabetes.
No. of patients:	
planned:	entered: 40 male and female patients with type 2 diabetes (MRD part)
actual:	entered: MRD part: 38 (36 male and 2 female patients) 0.5 mg BI 14332 CL: treated: 7 analysed (for primary endpoint): 7 2.5 mg BI 14332 CL: treated: 7 analysed (for primary endpoint): 7 10 mg BI 14332 CL: treated: 8 analysed (for primary endpoint): 8 20 mg BI 14332 CL: treated: 8 analysed (for primary endpoint): 8 placebo: treated: 8 analysed (for primary endpoint): 8 4-week treatment part: not performed

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Diagnosis and main criteria for inclusion:	Male and female (postmenopausal or hysterectomised) patients with type 2 diabetes, age ≥21 to ≤70 years or age ≥60 to ≤70 years (postmenopausal female patients), body mass index (BMI): ≥18.5 to ≤35 kg/m^2.
Test product:	BI 14332 CL
dose:	0.5 mg, 2.5 mg, 10 mg, 20 mg as tablets
mode of admin.:	oral administration
batch no.:	0.5 mg: B061001461 1 mg: B061001464 5 mg: B061001460
Duration of treatment:	14-day wash-out of previous anti-diabetic therapy followed by 10 days of once daily dosing at each dose level. The planned 4-week treatment part was cancelled.
Reference therapy:	placebo
dose:	matching placebo for each dose group
mode of admin.:	oral administration
batch no.:	B061001459, B061001465, and B061001463
Criteria for evaluation:	
Efficacy:	Pharmacodynamic parameters: dipeptidyl-peptidase 4 (DPP-4) inhibition and plasma glucose. Pharmacokinetic (PK) parameters: C_{max}, t_{max}, $AUC_{\tau,1}$, $AUC_{0\text{-}tz}$, $Ae_{0\text{-}24}$, $fe_{0\text{-}24}$, $CL_{R,0\text{-}24}$, $C_{pre,N}$, $C_{max,ss}$, $C_{min,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, $Ae_{\tau,ss}$, $fe_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$, $CL_{R,ss}$, $MRT_{po,ss}$, R_A, PTF, and additional parameters as appropriate. Attainment of steady-state and dose proportionality of PK parameters.
Safety:	Tolerability, adverse events, physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, and clinical laboratory tests.
Statistical methods:	Descriptive statistics for safety and PK endpoints were calculated. Dose proportionality of BI 14332 CL was explored using a regression model that described the functional relationship between the dose and the PK parameters C_{max}, $AUC_{\tau,1}$, $C_{trough,10}$, $C_{max,ss}$, and $AUC_{\tau,ss}$. A 95% confidence interval for the slope was computed. For the attainment of steady-state the trough concentration of BI 14332 CL was analysed by a mixed linear model with 'time' as a repeated effect. Subsequently, pair-wise comparisons of the differences between all time points were performed using t-tests.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics

In the dose range investigated, BI 14332 BS exhibited nonlinear pharmacokinetics, with a less than proportional increase in C_{max} and AUC from the 0.5 to 10 mg dose and a reasonable proportional increase between the 10 and 20 mg dose after multiple dosing. The maximum plasma concentration at steady-state ($C_{max,ss}$) was reached between 1.5 and 3 hours after study drug administration. Steady-state was reached within 5 days for all dose groups.
BI 14332 BS showed no to moderate dose dependent accumulation regarding AUC (Accumulation ratio R_A ~ 0.865 to 2.53), which decreased with increasing doses. The renal excretion of the parent compound seemed to be only a minor way of elimination and increased with dose from about 4.2% of the dose in the 0.5 mg dose group to about 10.1% of the dose in the 20 mg dose group.
BI 14332 BS showed a dose dependent clearance, increasing from 330 mL/min (0.5 mg) to 1620 mL/min (20 mg). The volume of distribution increased with dose from 3360 L (0.5 mg) to 13500 L (20 mg) and the terminal half-life at steady-state ranged from 83.2 hours to 118 hours.

Pharmacodynamics

All doses of BI 14332 CL administered in this multiple dose study resulted in an inhibition of DPP-4 activity in plasma. After 10 days of once daily treatment with BI 14332 CL, geometric mean plasma DPP-4 activity at trough was 62.8%, 20.8%, 10.1%, and 8.78% for the 0.5 mg, 2.5 mg, 10 mg, and 20 mg dose groups, respectively. While this indicates that increasing doses of BI 14332 CL had an additional effect on the inhibition of plasma DPP-4 activity, the maximum inhibitory effect was approached with the 10 mg dose (10.1% DPP-4 activity) and did not increase substantially when doubling the dose (8.78% DPP-4 activity for the 20 mg dose group). Based on visual assessment of trough concentrations, the treatment duration of 10 days did not result in a pharmacodynamic steady-state for the 0.5 mg and 2.5 mg dose groups. Overall, the inter-individual variability of plasma DPP-4 activity after multiple dosing was low to moderate over time and doses with the geometric coefficient of variation (gCV) being mostly in the range of 10-60%. BI 14332 BS plasma concentrations correlated with DPP-4 activity measured in plasma. Plasma concentrations of approximately 3 nmol/L resulted in a 50% inhibition and concentrations of about 5 nmol/L resulted in an 80% inhibition of the enzyme.

Furthermore, plasma glucose $AUEC_{0-3,BL,norm}$ values after an MTT on days 1 and 11 were decreased compared with placebo for all dose groups.

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Safety results:

There were no serious or other significant adverse events (AEs) and no one discontinued from the trial prematurely.

A total of 10 patients (26.3%) experienced at least 1 AE during the study: 1 patient during the screening period, 2 patients during wash-out, and 7 patients during the treatment phase. Of the 7 patients, who reported an AE during treatment, 1 patient was allocated to placebo and 6 patients were treated with BI 14332 CL at different dose levels. All AEs were of mild or moderate intensity. The most frequently reported AE was constipation with an overall incidence of 4 cases per 38 patients (10.5%). Three of the patients with constipation received the highest dose of 20 mg BI 14332 CL. These AEs were considered possibly related to the study drug by the investigator. One patient in the 2.5 mg dose group reported constipation that was not considered drug-related. All cases of constipation were mild in intensity. In addition to constipation, 1 patient in the 20 mg dose group experienced an episode of hypoglycaemia on day 11, the day after the last study drug administration (post-treatment period). The AE was most probably related to the MTT, which had been started 3 hours before. The patient was given glucose and recovered within the next hour.

The overall tolerability assessment, based on AEs and results of laboratory tests, was "good" for all patients. In addition, there were no clinically relevant findings with respect to the clinical laboratory parameters, ECG evaluation, vital signs, and the physical examination. No elevation of plasma histamine levels was observed.

Conclusions:

This was the first study with BI 14332 CL in patients with type 2 diabetes. BI 14332 CL was safe and well tolerated by all patients and within all dose groups (0.5 mg, 2.5 mg, 10 mg, and 20 mg). The most frequently reported AE was mild constipation, experienced by 3 patients in the 20 mg dose group and by 1 patient in the 2.5 mg dose group.

All doses of BI 14332 CL administered once daily for 10 days resulted in an inhibition of DPP-4 activity in plasma. The maximum inhibitory effect was achieved with the 10 mg dose. Measurements of DPP-4 activity correlated well with BI 14332 BS plasma concentrations. Plasma concentrations of approximately 3 nmol/L resulted in a 50% inhibition and concentrations of about 5 nmol/L resulted in an 80% inhibition of the enzyme.

The development of BI 14332 CL was discontinued in March 2007 due to favourable results of the leading DPP-4 inhibitor compound BI 1356. Therefore, the present study was prematurely terminated after completion of the MRD part.