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.:** 2008-006089-27	
Name of active ingredients: Linagliptin, BI 10773		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 August 2010	**Trial No. / U No.:** 1245.30 / U10-2248-01	**Dates of trial:** 07 JUL 2009 – 25 SEP 2009	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of multiple doses BI 10773 50 mg and linagliptin 5 mg after concomitant administration compared to multiple doses of BI 10773 50 mg and linagliptin 5 mg administered alone to healthy male volunteers (an open-label, randomised, crossover, clinical phase I study)
Principal Investigator:	[redacted]
Trial sites:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	Investigate the relative bioavailability of BI 10773 and of linagliptin after concomitant multiple oral administration of 50 mg BI 10773 tablets and 5 mg linagliptin in comparison to 50 mg BI 10773 and 5 mg linagliptin given alone
Methodology:	Open-label, randomised, multiple dose, crossover study with three treatment periods separated by a wash-out phase of at least 35 days (between treatments AB and treatment C and between treatment C and treatments AB)
No. of subjects:	
planned:	entered: 16
actual:	entered: 16 Treatment AB_C (BI 10773 / BI 10773+linagliptin / linagliptin): entered: 8 treated: 8 analysed (for primary endpoints): 8 Treatment C_AB (linagliptin / BI 10773 / BI 10773 + linagliptin): entered: 8 treated: 8 analysed (for primary endpoints): 8
Diagnosis and main criteria for inclusion:	Healthy male volunteers Age 18 to 50 years Body mass index 18.5 to 29.9 kg/m^2

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Test product 1:	BI 10773 25 mg tablet
dose:	50 mg (2 tablets of 25 mg)
mode of admin.:	Oral
batch no.:	B073000869
Test product 2:	Linagliptin 5 mg film-coated tablet
dose:	5 mg
mode of admin.:	Oral
batch no.:	P01005567
Duration of treatment:	BI 10773 alone was given once daily for 5 days (treatment A) BI 10773 and linagliptin were given once daily in combination for 7 days (treatment B) Linagliptin alone was given once daily for 7 days (treatment C) BI 10773 was given for a total of 12 consecutive days Linagliptin was given for a total of 14 days (2 periods of 7 days each) Washout after treatment B for sequence AB_C and after treatment C for sequence C_AB at least 35 days
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was relative bioavailability based on the area under the concentration-time curve of the analyte in plasma at steady-state over a uniform dosing interval τ ($AUC_{\tau,ss}$) and the maximum measured concentration of the analyte in plasma at steady-state over a uniform dosing interval τ ($C_{max,ss}$) for BI 10773 and linagliptin when co-administered and when given alone. A sensitivity analysis per sequence was performed for the primary endpoints. The secondary pharmacokinetic and pharmacodynamic endpoints were $t_{max,ss}$, urinary glucose excretion, and inhibition of dipeptidyl peptidase-4 (DPP-4) for BI 10773 and linagliptin. Attainment of steady state was investigated for both analytes.

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Safety:	The secondary safety endpoints were adverse events, physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), laboratory tests, and assessment of global tolerability.
Statistical methods:	The statistical model was analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects nested within sequences', 'period', and 'treatment'. Point estimators (geometric means) of the median intra-subject ratios of $AUC_{\tau,ss}$ and $C_{max,ss}$ and their two-sided 90% confidence intervals were calculated. Confidence intervals were based on the residual error from ANOVA. Descriptive statistics were calculated for all other parameters.

SUMMARY – CONCLUSIONS:

Pharmacokinetic/ pharmacodynamic results:

Pharmacokinetics

Pharmacokinetic steady state conditions were achieved within 5 days of administration of 50 mg BI 10773 once daily with or without linagliptin and within 7 days of administration of 5 mg linagliptin once daily with or without BI 10773. The geometric mean $AUC_{\tau,ss}$ of BI 10773 was similar when the drug was given with linagliptin (9390 nmol·h/L, 17.2% geometric coefficient of variation [gCV]) and when given alone (9230 nmol·h/L, 12.1% gCV) but geometric mean $C_{max,ss}$ was reduced from 1440 nmol/L (16.0 %gCV) when BI 10773 was given alone to 1270 nmol/L (27.1% gCV) when the drug was given with linagliptin. Median $t_{max,ss}$ of BI 10773 was slightly longer when the drug was given with linagliptin (1.5 h) than when given alone (1.0 h).

When linagliptin was given with BI 10773, geometric mean $C_{max,ss}$ was 11.2 nmol/L (28.6% gCV), compared with 11.0 nmol/L (30.3% gCV) when given alone. Geometric mean $AUC_{\tau,ss}$ of linagliptin was 158 nmol·h/L (14.7% gCV) when given with BI 10773 and 152 nmol·h/L (16.9% gCV) when given alone. Median $t_{max,ss}$ of linagliptin was 1.5 h for both treatments.

The cumulative amounts of BI 10773 and linagliptin excreted in urine were not affected by co-administration (20.4% of dose of BI 10773 given with linagliptin vs 20.7% of dose of BI 10773 alone; 4.8% of dose of linagliptin given with BI 10773 vs 4.3% of dose of linagliptin given alone).

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Pharmacokinetic/ pharmacodynamic results (continued):

The results of the bioavailability analysis for BI 10773 and linagliptin are displayed in the table below. The 90% confidence intervals of the adjusted geometric mean ratios of $C_{max,ss}$ and $AUC_{\tau,ss}$ of linagliptin and $AUC_{\tau,ss}$ of BI 10773 were within the bioequivalence acceptance limits of 80% to 125%. Geometric mean $C_{max,ss}$ of BI 10773 was reduced by approximately 12% when the drug was co-administered with linagliptin.

Analysis of relative bioavailability of BI 10773 and linagliptin

Parameter	Test (N=16)	Reference (N=16)	Adjusted gMean Ratio (Test/Reference) [%]	Two-sided 90% confidence interval	
				Lower limit [%]	Upper limit [%]
$AUC_{\tau,ss}$ [nmol·h/L]	BI 10773 + Linagliptin	BI 10773	101.7	96.5	107.2
$C_{max,ss}$ [nmol/L]	BI 10773 + Linagliptin	BI 10773	88.3	78.8	98.9
$AUC_{\tau,ss}$ [nmol·h/L]	BI 10773 + Linagliptin	Linagliptin	103.3	96.1	111.1
$C_{max,ss}$ [nmol/L]	BI 10773 + Linagliptin	Linagliptin	101.5	86.9	118.5

Pharmacodynamics

DPP-4 inhibition was assessed as a surrogate marker of the effect of linagliptin. Trough DPP-4 inhibition ($E_{24,ss}$) was similar when linagliptin was administered with BI 10773 compared with linagliptin alone (median $E_{24,ss}$ 83.9% vs 83.7%). BI 10773 alone had no effect on DPP-4 activity.

Urinary glucose excretion over 24 h was assessed as a surrogate marker of the effect of BI 10773. The mean (± SD) cumulative amount of glucose excreted in urine over 24 h (Ae_{0-24}) was approximately 18% lower when BI 10773 was administered with linagliptin (54.8 ± 11.2 g) than when the drug was given alone (67.2 ± 14.6 g). When linagliptin was given alone, urinary glucose excretion was negligible.

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Safety results:	No subjects experienced adverse events during treatment with 50 mg BI 10773 once daily (q.d.) and 5 mg linagliptin q.d. for 7 days. One subject (6.3%) experienced an adverse event during treatment with 50 mg BI 10773 q.d. for 5 days and 5 subjects (31.3%) experienced at least 1 adverse event during treatment with 5 mg linagliptin q.d. for 7 days; however, only 1 subject (treated with linagliptin) experienced an adverse event (headache) which the investigator considered related to the study medication. All adverse events were of mild or moderate intensity. No subjects experienced serious or other significant adverse events and no subjects discontinued the study medication. The most frequently reported adverse events were headache and nasopharyngitis (2 subjects each, 12.5%). Slight reductions in mean blood glucose were observed in all treatment groups but no subjects experienced hypoglycaemia during the study. As expected, increases in urinary glucose were observed in subjects treated with BI 10773 with and without linagliptin but not in subjects treated with linagliptin alone. No clinically relevant changes in other laboratory parameters, vital signs, or ECG were observed. Global tolerability was good in all subjects.
Conclusions:	The steady state bioavailability of 5 mg linagliptin q.d. (based on $AUC_{\tau,ss}$ and $C_{max,ss}$) was not affected by concomitant administration of 50 mg BI 10773 q.d., as the 90% confidence intervals of the adjusted geometric mean ratios were completely located within the generally applied bioequivalence acceptance limits of 80 to 125%. The $AUC_{\tau,ss}$ of BI 10773 was similar when the drug was given alone and in combination with linagliptin but the $C_{max,ss}$ of BI 10773 was reduced by approximately 12% when the drug was given with linagliptin. The combination of 50 mg BI 10773 q.d. and 5 mg linagliptin q.d. was safe and well tolerated. It can be concluded that BI 10773 and linagliptin can be co-administered without dose adjustment and there are no safety concerns for future clinical trials of this combination.