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.:** 2008-006088-35	
Name of active ingredient: BI 10773		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 FEB 2010	**Trial No. / U No.:** 1245.27 / U10-1274-02	**Dates of trial:** 19 MAY 2009 – 11 JUL 2009	**Date of revision:** 03 NOV 2011

Title of trial:	Relative bioavailability of both BI 10773 and sitagliptin after co-administration compared to multiple oral doses of BI 10773 (50 mg q.d.) alone and sitagliptin (100 mg q.d.) alone in healthy male volunteers (an open-label, randomised, crossover, clinical phase I study)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Biberach, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objective:	The objective was to investigate whether there was a drug-drug interaction between BI 10773 and sitagliptin when co-administered as multiple oral doses. Therefore, the relative bioavailabilities of BI 10773 and sitagliptin were determined when both drugs were given in combination compared with BI 10773 or sitagliptin given alone.
Methodology:	The study was conducted according to an open-label, randomised, multiple-dose, crossover design with 3 treatments (A, B, C) and 2 treatment sequences (AB_C or C_AB).
No. of subjects:	
planned:	entered: 16
actual:	entered: 16 Treatment A: BI 10773 50 mg once daily treated: 16 analysed (for primary endpoints): 16 Treatment B: BI 10773 50 mg once daily plus sitagliptin 100 mg once daily treated: 16 analysed (for primary endpoints): 16 Treatment C: sitagliptin 100 mg once daily treated: 16 analysed (for primary endpoints): 16
Diagnosis and main criteria for inclusion:	Healthy male subjects of 18 to 50 years with a body mass index (BMI) of 18.5 to 29.9 kg/m² were included in the study.

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Test product:	BI 10773 tablets	
dose:	50 mg once daily (given as two 25 mg tablets)	
mode of admin.:	Oral	
batch no.:	B073000869	
Reference therapy:	Sitagliptin tablets (Januvia®)	
dose:	100 mg once daily	
mode of admin.:	Oral	
batch no.:	B091000116 (MSD Sharp & Dohme GmbH)	
Duration of treatments:	BI 10773 was administered for 5 days (treatment A), immediately followed by co-administration of BI 10773 and sitagliptin over additional 5 days (treatment B). In treatment C, sitagliptin alone was administered for 5 days. Treatments AB and C were separated by a wash-out period of at least 7 days in each treatment sequence (AB_C and C_AB).	
Criteria for evaluation:		
Clinical pharmacology:	Primary endpoints:	$AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 and sitagliptin co-administered and given alone
	Secondary endpoints:	Pharmacokinetics: $C_{24,N}$, $\lambda_{z,ss}$, $t_{½,ss}$, $t_{max,ss}$, $MRT_{po,ss}$, CL/F_{ss}, V_z/F_{ss}, $Ae_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss}$, $CL_{R,ss}$ of BI 10773 and sitagliptin Pharmacodynamics: $UGE_{0\text{-}24}$
Safety:	The safety evaluation was based on physical examinations, monitoring of vital signs (blood pressure, pulse rate), 12-lead electrocardiograms (ECG), clinical laboratory tests (haematology, clinical chemistry, and urinalysis), the analysis of adverse events (AEs), and an assessment of tolerability by the investigator.	
Statistical methods:	Point estimators (geometric means [gMean]) of the median intra-subject ratios of $AUC_{\tau,ss}$ and $C_{max,ss}$ and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model used for the comparison of the sitagliptin-containing treatments (treatments B and C) was an analysis of variance (ANOVA) model on log-transformed parameters including effects for 'sequence',	

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'subjects within sequences', 'period', and 'treatment'. The model used for the comparison of the BI 10773-containing treatments (treatments A and B) was an ANOVA model on the logarithmic scale, with terms for 'subject' and 'treatment'. CIs were based on the residual error from the ANOVA. The attainment of steady-state was investigated for both BI 10773 and sitagliptin. For $AUC_{\tau,ss}$, $C_{max,ss}$ and all other parameters, descriptive statistics were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

All 16 randomised subjects completed the trial according to the Clinical Trial Protocol.

For BI 10773, there were no major differences in mean steady-state $AUC_{\tau,ss}$ and $C_{max,ss}$ when BI 10773 was administered with and without sitagliptin: $AUC_{\tau,ss}$ 9280 nmol·h/L vs. 8430 nmol·h/L and $C_{max,ss}$ 1260 nmol/L vs. 1180 nmol/L. Mean $t_{max,ss}$ of BI 10773 was approximately 2 h for either treatment. Mean $AUC_{\tau,ss}$ and $C_{max,ss}$ of sitagliptin were also comparable with and without BI 10773 co-administration: $AUC_{\tau,ss}$ 2680 ng·h/mL vs. 2600 ng·h/mL and $C_{max,ss}$ 370 ng/mL vs. 341 ng/mL. Mean $t_{max,ss}$ of sitagliptin was similar with (2.73 h) and without co-administration (2.62 h).

The following table summarises the adjusted gMean Test/Reference ratios and 90% CIs for $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 and sitagliptin.

Parameter	**Test**	**Reference**	**Adjusted gMean ratio Test/Reference** [%]	**2-sided 90% confidence interval Lower limit** [%]	**Upper limit** [%]
BI 10773					
$AUC_{\tau,ss}$	BI 10773+sitagliptin	BI 10773	110.39	103.91	117.27
$C_{max,ss}$	BI 10773+sitagliptin	BI 10773	107.61	97.01	119.37
Sitagliptin					
$AUC_{\tau,ss}$	BI 10773+sitagliptin	sitagliptin	103.06	98.95	107.34
$C_{max,ss}$	BI 10773+sitagliptin	sitagliptin	108.48	100.68	116.88

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The results of the bioavailability analysis show that co-administration of BI 10773 with sitagliptin did not affect the extent and rate of absorption of BI 10773. Intra-individual variability between the treatments was low for both $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 (geometric coefficients of variation [gCV] 9.8% and 16.9%, respectively). Co-administration of both drugs did not affect the extent and rate of absorption of sitagliptin either. For $AUC_{\tau,ss}$ of sitagliptin, the intra-individual gCV was 6.5%, for $C_{max,ss}$ of sitagliptin, the intra-individual gCV was 12.0%. The extent and rate of absorption met the standard bioequivalence criteria of 80% to 125% for both BI 10773 and sitagliptin.

The cumulative amounts of BI 10773 and sitagliptin excreted in urine were not affected by co-administration (BI 10773: 17.1% of dose without vs. 19.3% of dose with co-administration; sitagliptin: 60.3% of dose without vs. 62.8% of dose with co-administration).

In addition, there were no clinically relevant differences in the mean cumulative amounts of glucose excreted in urine (UGE_{0-24}) when BI 10773 was administered with and without sitagliptin (62.6 g and 73.4 g, respectively).

Safety results:

All 16 subjects received a total dose of 500 mg of BI 10773 (50 mg once daily) and a total dose of 1000 mg of sitagliptin (100 mg once daily) during the trial as planned.

Five subjects (31.3%) reported at least 1 AE: 3 subjects (18.8%) each during treatment with BI 10773 alone (diarrhoea/loose stool, glossodynia) and sitagliptin alone (rash, nausea, vomiting, headache), respectively. No AEs were reported during the co-administration treatment period (BI 10773 plus sitagliptin).

The most frequently reported AEs overall were diarrhoea/loose stool (18.8% of all subjects) and headache (12.5% of all subjects). Diarrhoea/loose stool occurred during BI 10773 treatment alone (3 subjects) and headache during sitagliptin treatment alone (2 subjects). Other AEs reported during the trial were nausea, vomiting, glossodynia, and rash, experienced by 1 subject (6.3%) each. No subject experienced an AE that was judged as drug-related by the investigator.

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Conclusions:

Most reported AEs were of mild or moderate intensity, only 1 subject experienced an AE of severe intensity (headache under sitagliptin treatment). No serious AEs and no AEs leading to discontinuation occurred in this trial. None of the AEs required therapy and all subject recovered fully.

Overall tolerability was assessed as 'good' for all 16 subjects in each treatment period. There were no clinically relevant findings with respect to the evaluation of laboratory parameters, blood glucose tests, vital signs, and ECG recordings.

Sitagliptin co-administration had no clinically relevant effect on either the extent or rate of absorption of BI 10773, as determined by the standard bioequivalence boundaries. Similarly, BI 10773 co-administration had no clinically relevant effect on either the extent or rate of absorption of sitagliptin, as determined by the standard bioequivalence boundaries. Renal clearance of both BI 10773 and sitagliptin were also similar with and without co-administration. The results demonstrate that there is no drug-drug interaction between BI 10773 and sitagliptin.

Furthermore, multiple daily doses of 50 mg BI 10773 and 100 mg sitagliptin were well tolerated when given either alone or in combination to healthy male subjects.