Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-019211-38	
Name of active ingredients: BI 10773 / linagliptin		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 MAY 2011	**Trial No. / U No.:** 1275.3 / U11-1690-01	**Dates of trial:** 23 AUG 2010 – 30 NOV 2010	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability investigations of a 25 mg BI 10773 / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomised, single dose, crossover, Phase I trial in healthy male and female volunteers)
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
Objectives:	The objectives were to determine the relative bioavailability of a 25 mg BI 10773 / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1: 'FDC A1') compared with the individual tablets administered together and a second formulation of the FDC tablet (formulation A3: 'FDC A3') as well as to assess the effect of food on the bioavailability of the FDC A1 tablet.
Methodology:	Open-label, randomised, single-dose, crossover design (with two 3-way crossover parts). Each subject was to receive 3 of the 4 treatments investigated.
No. of subjects:	
planned:	entered: 42 (including 18 for the food effect part and 24 for the comparison of 2 different formulations of the FDC tablet)
actual:	entered: 42 Treatment A: FDC A1 tablet: treated: 42 analysed (for primary endpoints): 42 Treatment B: BI 10773 and linagliptin individual tablets: treated: 41 analysed (for primary endpoints): 40 Treatment C: FDC A1 tablet, fed conditions: treated: 18 analysed (for primary endpoints): 18 Treatment D: FDC A3 tablet: treated: 24 analysed (for primary endpoints): 24

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Diagnosis and main criteria for inclusion:	Healthy volunteers, male and female, age 18 to 55 years, body mass index (BMI) 18.5 to 29.9 kg/m^2
Test/reference products:	A: BI 10773/linagliptin FDC A1 tablet (formulation with normal dissolution) B: BI 10773 and linagliptin individual tablets administered together C: BI 10773/linagliptin FDC A1 tablet, fed conditions D: BI 10773/linagliptin FDC A3 tablet (slow dissolving formulation)
dose:	25 mg BI 10773, 5 mg linagliptin
mode of admin.:	A: oral, fasted B: oral, fasted C: oral, after a high-fat, high-caloric meal D: oral, fasted
batch no.:	A: B101003361 B: 909473A (BI 10773) and 4000044 (linagliptin) C: B101003361 D: B101003271
Duration of treatment:	The subjects were to undergo 3 treatment periods and were to receive a single dose of trial medication in each treatment period. The 3 drug administrations were separated by washout phases of at least 35 days.
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters of BI 10773 and linagliptin: Primary endpoints: AUC_{0-tz} and C_{max} for BI 10773; AUC_{0-72} and C_{max} for linagliptin Secondary endpoints: t_{max}, $AUC_{0-\infty}$, and other pharmacokinetic characteristics for BI 10773 and linagliptin
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, adverse events (AEs), tolerability assessment
Statistical methods:	The geometric mean (gMean) point estimators for the median intrasubject ratios of AUC (Test) to AUC (Reference) and of C_{max} (Test) to C_{max} (Reference) and their 2-sided 90% confidence intervals were calculated. The statistical model was an analysis of variance model (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and

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'treatment'. While the effect 'subjects within sequences' was a random effect, the other effects were considered fix. The following comparisons were made: FDC A1 (Test) versus individual tablets (Reference), FDC A1 fed (Test) versus FDC A1 fasted (Reference), FDC A3 (Test) versus FDC A1 (Reference).

For all pharmacokinetic parameters and certain safety parameters, descriptive statistics were calculated. Frequencies are tabulated for categorical parameters.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

The study population consisted of 42 healthy subjects, 25 female and 17 male. Forty-one subjects were White and 1 subject was Black. The mean age was 40.3 years, ranging from 19 to 55 years, and the mean BMI was 23.40 kg/m^2. Forty-one subjects completed all 3 treatment periods whereas 1 subject discontinued the study due to AEs after the second treatment period.

BI 10773 and linagliptin gMean plasma concentration-time profiles were similarly shaped for the 4 treatments. However, profiles after administration of the FDC A1 tablet in the fed state displayed lower maximum concentration values that occurred slightly later compared with the other 3 treatments.

Geometric mean AUC_{0-tz} of BI 10773 was comparable for the 4 treatments with 5990 nmol·h/L (FDC A1), 5720 nmol·h/L (individual tablets), 5400 nmol·h/L (FDC A1 fed), and 5490 nmol·h/L (FDC A3). Geometric mean C_{max} of BI 10773 was comparable for the FDC A1 tablet (862 nmol/L), the individual tablets (803 nmol/L), and the FDC A3 tablet (787 nmol/L), but was reduced when the FDC A1 tablet was given in the fed state (583 nmol/L). Following drug administration, maximum BI 10773 plasma concentrations were observed at a median t_{max} of 1.50 h (FDC A1), 1.25 h (individual tablets), 2.00 h (FDC A1 fed), and 1.50 h (FDC A3).

Geometric mean AUC_{0-72} of linagliptin was also comparable for the 4 treatments with 264 nmol·h/L (FDC A1), 250 nmol·h/L (individual tablets), 250 nmol·h/L (FDC A1 fed), and 247 nmol·h/L (FDC A3). Geometric mean C_{max} of linagliptin was comparable for the FDC A1 tablet (8.19 nmol/L), the individual tablets (7.49 nmol/L), and the FDC A3 tablet (7.93 nmol/L), but was reduced when the FDC A1 tablet was given in the fed state (6.14 nmol/L). Following drug administration, maximum linagliptin plasma concentrations were observed at a median t_{max} of 1.50 h (FDC A1), 1.75 h (individual tablets), 2.25 h (FDC A1 fed), and 1.50 h (FDC A3).

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Clinical pharmacology results (cont.)

The results of the relative bioavailability analyses for the primary parameters of BI 10773 and linagliptin are presented in the following table.

	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90% confidence interval		Intraindividual gCV [%]
		Lower limit [%]	Upper limit [%]	
Comparison FDC A1 tablet (N=42) vs. individual tablets (N=40)				
BI 10773				
AUC_{0-tz}	104.9	102.1	107.8	7.2
C_{max}	107.7	101.7	114.0	15.3
Linagliptin				
AUC_{0-72}	104.9	100.0	110.1	12.8
C_{max}	109.7	99.6	120.8	26.2
Comparison FDC A1 tablet fed (N=18) vs. FDC A1 tablet fasted (N=18)				
BI 10773				
AUC_{0-tz}	85.3	80.8	90.1	9.4
C_{max}	61.4	54.1	69.7	22.0
Linagliptin				
AUC_{0-72}	91.0	84.2	98.2	13.2
C_{max}	68.5	58.6	80.0	27.2
Comparison FDC A3 tablet (N=24) vs. FDC A1 tablet (N=24)				
BI 10773				
AUC_{0-tz}	95.7	91.2	100.4	9.8
C_{max}	98.0	92.0	104.5	13.0
Linagliptin				
AUC_{0-72}	96.4	89.8	103.4	14.3
C_{max}	103.7	92.9	115.7	22.4

The 90% confidence intervals for AUC and C_{max} of BI 10773 and linagliptin were within the standard acceptance range for bioequivalence of 80 to 125% when the FDC A1 tablet was compared with the individual tablets, and also when the 2 different formulations of the FDC tablet were compared.

When the FDC A1 tablet was administered in the fed state, AUC was reduced by 15% for BI 10773 and by 9% for linagliptin, and C_{max} was reduced by 39% for BI 10773 and by 32% for linagliptin compared with the same tablet taken while fasted. Since AUC is considered more relevant than C_{max} and the 90% confidence intervals for AUC of both analytes were fully contained within the acceptance range of 80 to 125%, the effect of food on C_{max} was not considered clinically relevant.

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Safety results:

Forty-one subjects were administered a total dose of 75 mg BI 10773 and a total dose of 15 mg linagliptin during the trial as planned. The subject who discontinued after the second treatment period received a total dose of 50 mg BI 10773 and 10 mg linagliptin.

Twenty-three subjects (54.8%) reported at least 1 AE during the study: 12 subjects (28.6%) in the treatment period with the FDC A1 tablet, 6 subjects (14.6%) in the treatment period with the individual tablets, 6 subjects (33.3%) in the treatment period with the FDC A1 tablet given in the fed state, and 6 subjects (25.0%) in the treatment period with the FDC A3 tablet.

On the preferred term level, the most frequently reported AEs overall were headache (9 subjects, 21.4%), nasopharyngitis (5 subjects, 11.9%), vomiting (5 subjects, 11.9%), and nausea (3 subjects, 7.1%). For 6 subjects (14.3%), AEs of severe intensity were reported: influenza, back pain, contusion of chest wall, nausea, and 2 cases of headache. Eleven subjects (26.2%) reported AEs that the investigator considered possibly related to the study medication. The most frequent drug-related AEs were headache (8 subjects, 19.0%) and vomiting (3 subjects, 7.1%). Nausea and dizziness were assessed as drug-related in 2 subjects (4.8%) each, dry mouth in 1 subject (2.4%).

No deaths, other SAEs, or other significant AEs were reported in the study. One female subject reported mild headache in the treatment period with the FDC A1 tablet as well as severe nausea and moderate vomiting in 2 treatment periods (FDC A1 and FDC A3). The subject discontinued the trial due to these AEs after the second treatment period. The AEs were not considered as leading to treatment discontinuation and thus not as ‘other significant’ (ICH E3 definition), as the treatment in a single-dose trial could not be discontinued or reduced in dose.

For the subject who discontinued the trial due to AEs, the assessment of tolerability after the second treatment period was ‘satisfactory’. For all other subjects, the assessment of tolerability was ‘good’ in each treatment period.

The clinical laboratory evaluation did not reveal any clinically relevant changes in laboratory parameters and there were no findings with respect to vital signs or ECG recordings.

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Conclusions:

The 90% confidence intervals for AUC and C_{max} of BI 10773 and linagliptin were within the standard acceptance range for bioequivalence of 80 to 125% when the 25 mg BI 10773 / 5 mg linagliptin FDC A1 tablet was compared with the individual tablets of BI 10773 and linagliptin administered together. Thus, the FDC A1 tablet and the individual tablets can be considered bioequivalent. There was also no difference with regard to AUC and C_{max} between the FDC tablet with normal dissolution (FDC A1) and a slow dissolving formulation (FDC A3). Administration of the FDC A1 tablet in the fed state reduced the peak exposure of BI 10773 and linagliptin but did not influence the total exposure. The FDC tablet may therefore be administered with or without food.

Single doses of 25 mg BI 10773 and 5 mg linagliptin were safe and well tolerated in the majority of subjects when administered as FDC A1 tablet in the fed and fasted state, as individual tablets, or as FDC A3 tablet.