Boehringer Ingelheim

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.

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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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005142-11	
BI Investigational Product: Linagliptin (BI1356)/metformin extended release (fixed dose combination)		**Page:** 1 of 5	
Report Date: 13 Feb 2015	**Trial No. / Doc. No.:** 1288.9 / c02895304-01	**Dates of Trial:** 13 May 2014 - 31 Jul 2014	**Date of Revision:** Not applicable

Title of Trial:	Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised, single dose, two-way crossover trial)
Principal Investigator:	[redacted]
Trial Sites:	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine and Clinical Pharmacology, Human Pharmacology Centre, Birkendorfer Str. 65, Biberach/Riss, Germany
Publications:	Data from this trial have not been published at the time of this clinical trial report.
Clinical Phase:	I
Objectives:	The objective was to establish the bioequivalence of linagliptin/metformin extended release (XR) fixed dose combination (FDC) tablets versus the free combination of linagliptin tablets and metformin XR tablets under fasted (Part 1) and fed (Part 2) conditions.
Methodology:	This was a randomised, open-label, single-dose, 2-way crossover trial with 2 individual study parts: Part 1: one 5 mg linagliptin/1000 mg metformin XR FDC tablet versus the free combination (1 tablet 5 mg linagliptin and 2 tablets 500 mg metformin XR) under fasted conditions Part 2: one 5 mg linagliptin/1000 mg metformin XR FDC tablet versus the free combination (1 tablet 5 mg linagliptin and 2 tablets 500 mg metformin XR) under fed conditions
No. of Subjects:	
Planned:	Entered: 68 (52 under fasted conditions; 16 under fed conditions)
Actual:	Entered: 68 (52 under fasted conditions; 16 under fed conditions) Part 1 (fasted conditions): FDC: Treated: 52 Analysed (for primary endpoints): 52 Free combination: Treated: 52 Analysed (for primary endpoints): 52 Part 2 (fed conditions): FDC: Treated: 14 Analysed (for primary endpoints): 14 Free combination: Treated: 15 Analysed (for primary endpoints): 15

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Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male and female subjects, age 18 to 55 years, body mass index (BMI) 18.5 to 29.9 kg/m^2
BI Investigational Product:	5 mg linagliptin/1000 mg metformin XR FDC tablet
Dose:	5 mg linagliptin/1000 mg metformin XR (given as 1 FDC tablet)
Mode of Admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study part and after a high-fat, high-calorie meal for the fed study part
Batch No.:	B141000803
Comparator Products:	Comparator product 1: Tradjenta® (5 mg linagliptin tablet) Comparator product 2: Glumetza® (500 mg metformin XR tablet)
Dose:	5 mg linagliptin and 1000 mg metformin XR (given as 1 tablet 5 mg linagliptin and 2 tablets 500 mg metformin XR)
Mode of Admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study part and after a high-fat, high-calorie meal for the fed study part
Batch No.:	Tradjenta® 5 mg: B141000802 Glumetza® 500 mg: B141000801
Duration of Treatment:	Single dose for each treatment
Criteria for Evaluation:	
Clinical Pharmacology:	The following pharmacokinetic parameters were evaluated as primary endpoints: AUC_{0-72} and C_{max} for linagliptin, AUC_{0-tz} and C_{max} for metformin The following pharmacokinetic parameters were evaluated as secondary endpoints: $AUC_{0-\infty}$ for both linagliptin and metformin
Safety:	The evaluation of safety was based on: adverse events (including clinically relevant findings from the physical examination), safety laboratory tests, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG)

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Statistical Methods:

The assessment of bioequivalence was based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (FDC/free combination) for the primary endpoints using an acceptance range of 80.00 to 125.00%. This method is equivalent to the two 1-sided t-tests procedure, each at the 5% significance level. The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints. No interim analysis was performed.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 68 healthy volunteers participated in the study.

Fifty-two subjects participated in Part 1, all of whom completed the study as planned. Twenty-three study participants were male (44.2%) and 29 were female (55.8%). Age ranged from 19 to 54 years (mean: 34.7 years, standard deviation [SD]: 10.4 years), and BMI ranged from 19.1 to 29.1 kg/m^2 (mean: 23.93 kg/m^2, SD: 2.47 kg/m^2).

Sixteen subjects participated in Part 2, three of whom prematurely discontinued study participation. Two subjects discontinued due to adverse events: 1 subject after having been treated with the free combination and 1 subject after having been treated with the FDC in the first treatment period. One subject withdrew consent after having been treated with the free combination. Six study participants were male (37.5%) and 10 were female (62.5%). Age ranged from 18 to 53 years (mean: 36.1 years, SD: 11.9 years), and BMI ranged from 19.6 to 29.1 kg/m^2 (mean: 24.54 kg/m^2, SD: 2.96 kg/m^2).

All 68 subjects in this study were White. No relevant medical history or baseline conditions were reported for any of the participating subjects. All subjects were treated with at least 1 dose of study medication. No important protocol violations were reported.

Clinical Pharmacology Results:

Geometric mean (gMean) plasma concentration-time profiles and pharmacokinetic parameters of linagliptin and metformin were similar for the FDC and the free combination in each study part. The adjusted gMean values, the adjusted gMean ratios (FDC to free combination), 2-sided 90% CIs, and intra-subject geometric coefficient of variation (gCV) values for all primary and secondary endpoints are summarised in Table 1 below.

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Clinical Pharmacology Results (cont.):

For each study part, the adjusted gMean ratios FDC to free combination for the primary endpoints (AUC_{0-72} and C_{max} of linagliptin and AUC_{0-tz} and C_{max} of metformin) were close to 100%, with their corresponding 90% CIs within the pre-defined acceptance range for bioequivalence of 80.00 to 125.00%. The adjusted gMean ratios for the secondary endpoint, $AUC_{0-\infty}$ of linagliptin and metformin, were close to 100%, with their corresponding 90% CIs within the acceptance range for bioequivalence, except for $AUC_{0-\infty}$ of linagliptin under fed conditions, for which the lower limit of the 90% CI was outside the bioequivalence limit.

Table 1: Analysis of bioequivalence of linagliptin and metformin after administration of 5 mg linagliptin and 1000 mg metformin XR as FDC or free combination

Analyte Parameter	Adjusted gMean FDC	Adjusted gMean free combination	Adjusted gMean ratio FDC/free combination [%]	90% CI (upper limit, lower limit) [%]	Intra-individual gCV [%]
Part 1 (fasted conditions)					
Linagliptin (FDC N=52, free combination N=52)					
AUC_{0-72} [nmol·h/L]	288	287	100.4	(96.6, 104.3)	11.8
C_{max} [nmol/L]	9.54	8.83	108.1	(99.0, 118.0)	27.1
$AUC_{0-\infty}$ [nmol·h/L]	460	461	99.7	(95.2, 104.5)	14.3
Metformin (FDC N=52, free combination N=52)					
AUC_{0-tz} [ng·h/mL]	7146	7147	100.0	(93.0, 107.5)	22.2
C_{max} [ng/mL]	924	926	99.8	(92.5, 107.6)	23.4
$AUC_{0-\infty}$ [ng·h/mL]	7540	7608	99.1	(92.4, 106.4)	21.7
Part 2 (fed conditions)					
Linagliptin (FDC N=14, free combination N=15)					
AUC_{0-72} [nmol·h/L]	222	234	94.7	(88.7, 101.1)	9.2
C_{max} [nmol/L]	5.69	5.79	98.2	(94.1, 102.6)	6.1
$AUC_{0-\infty}$ [nmol·h/L]	387	398	97.4	(77.1, 123.0)	32.4
Metformin (FDC N=14, free combination N=15)[1]					
AUC_{0-tz} [ng·h/mL]	10 980	11 326	97.0	(92.2, 101.9)	7.1
C_{max} [ng/mL]	938	947	99.0	(95.0, 103.2)	5.9
$AUC_{0-\infty}$ [ng·h/mL][1]	14 774	15 047	98.2	(93.3, 103.3)	7.2

[1] One subject excluded from $AUC_{0-\infty}$ calculation for the FDC (FDC N=13, free combination N=15)

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Safety Results:

During the treatment periods of the 2 study parts, adverse events (AEs) were reported for a total of 26 subjects (38.2%). No deaths, protocol-specified adverse events of special interest (AESIs), or other significant AEs according to ICH E3 were reported in this study. All AEs had either resolved by the end of the study or had been sufficiently followed-up. There were no clinically relevant findings with respect to safety laboratory tests, vital signs, or ECG.

In Part 1, AEs were reported for 10 of 52 subjects (19.2%) during the treatment period with the free combination and for 13 of 52 subjects (25.0%) during the treatment period with the FDC tablet. All AEs were of mild or moderate intensity; no serious adverse events (SAEs) were reported in this study part. Four subjects (7.7%) reported AEs that were assessed as drug-related by the investigator (headache and diarrhoea). AEs reported for more than 1 subject in this study part at the preferred term level were headache (7 subjects, 13.5%), diarrhoea (4 subjects, 7.7%), dizziness, rhinitis, nasopharyngitis, and back pain (reported for 2 subjects each, 3.8%).

In Part 2, AEs were reported for 5 of 15 subjects (33.3%) during the treatment period with the free combination and for 4 of 14 subjects (28.6%) during the treatment period with the FDC tablet. Two subjects were reported with SAEs after treatment with the free combination: 1 subject had a fall and 1 subject had a road traffic accident, 26 and 15 days after the day of drug intake, respectively. The SAEs were severe in intensity; all other AEs were of mild or moderate intensity. One subject terminated the study prematurely after treatment with the FDC due to a suspected drug-induced allergic skin reaction (rash). Five subjects (31.3%) reported AEs that were assessed as drug-related by the investigator (headache, decreased appetite, vertigo, diarrhoea, abdominal discomfort, and rash). The most frequently reported AE (reported for more than 1 subject) in this study part at the preferred term level was headache (2 subjects, 12.5%).

Conclusions:

The fixed-dose combination tablet of 5 mg linagliptin/1000 mg metformin XR was bioequivalent to single tablets 5 mg linagliptin and 1000 mg metformin XR administered together, both under fasted and fed conditions. All adjusted geometric mean ratios FDC/free combination for AUC_{0-72} and C_{max} of linagliptin, and AUC_{0-tz} and C_{max} of metformin were close to 100% with their corresponding 90% CIs within the pre-defined acceptance range of 80.00 to 125.00%. All treatments investigated in this study were safe and well tolerated in healthy male and female subjects.