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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Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005143-85	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 1 of 6	
Report Date: 18 FEB 2015	**Trial No. / Doc. No.:** 1288.10 / c02895437-01	**Dates of Trial:** 16 May 2014 - 30 Jul 2014	**Date of Revision:** Not applicable

Title of Trial:	Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (2.5 mg/750 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, Binger Straße 173, Ingelheim, 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: two 2.5 mg linagliptin/750 mg metformin XR FDC tablets versus the free combination (1 tablet 5 mg linagliptin and 3 tablets 500 mg metformin XR) under fasted conditions Part 2: two 2.5 mg linagliptin/750 mg metformin XR FDC tablets versus the free combination (1 tablet 5 mg linagliptin and 3 tablets 500 mg metformin XR) under fed conditions
No. of Subjects:	
Planned:	Entered: 74 (58 under fasted conditions; 16 under fed conditions)
Actual:	Entered: 74 (58 under fasted conditions; 16 under fed conditions) Part 1 (fasted conditions): FDC: Treated: 58 Analysed (AUC_{0-72}, AUC_{0-tz}): 52 (linagliptin), 53 (metformin) Analysed (C_{max}): 53 (linagliptin), 54 (metformin)

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No. of Subjects (cont.):	Free combination: Treated: 58 Analysed (AUC_{0-72} and AUC_{0-tz}): 55 (linagliptin and metformin) Analysed (C_{max}): 56 (linagliptin and metformin) Part 2 (fed conditions): FDC: Treated: 16 Analysed (for primary endpoints): 14 (linagliptin), 15 (metformin) Free combination: Treated: 16 Analysed (for primary endpoints): 16 (linagliptin and metformin)
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:	2.5 mg Linagliptin/750 mg metformin XR FDC tablet
Dose:	5 mg linagliptin and 1500 mg metformin XR (given as 2 FDC tablets)
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.:	B141000806
Comparator Products:	Comparator product 1: Tradjenta® (5 mg linagliptin tablet) Comparator product 2: Glumetza® (500 mg metformin XR tablet)
Dose:	5 mg linagliptin and 1500 mg metformin XR (given as 1 tablet 5 mg linagliptin and 3 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: B141000805 Glumetza® 500 mg: B141000804
Duration of Treatment:	Single dose for each treatment

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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)

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 74 healthy volunteers participated in the study. Fifty-eight subjects participated in Part 1, six of whom prematurely discontinued study participation. Three subjects withdrew their consent after having been treated with the free combination. Two subjects discontinued due to adverse events (1 subject treated with the free combination and 1 subject with the FDC). One subject was withdrawn as a precaution due to other reasons after having been treated with the FDC. Twenty-eight study participants were male (48.3%) and 30 were female (51.7%). Age ranged from 19 to 54 years (mean: 39.0 years, standard deviation [SD]: 9.6 years), and BMI ranged from 18.6 to 29.9 kg/m^2 (mean: 25.24 kg/m^2, SD: 2.89 kg/m^2). No important protocol violations were reported in Part 1.

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Trial Subjects and Compliance with Trial Protocol (cont.):	Sixteen subjects participated in Part 2, all of whom completed the study as planned. Seven study participants were male (43.8%) and 9 were female (56.3%). Age ranged from 23 to 53 years (mean: 42.8 years, SD: 10.1 years), and BMI ranged from 21.1 to 29.1 kg/m^2 (mean: 24.74 kg/m^2, SD: 2.46 kg/m^2). One subject was reported with an important protocol violation (failed to eat the whole high-fat, high-calorie breakfast in Treatment period 2); this subject's data were excluded from pharmacokinetic analysis and descriptive statistics of the affected study period. All 74 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.
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. 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

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Clinical Pharmacology Results (cont.):

Table 1: Analysis of bioequivalence of linagliptin and metformin after administration of 5 mg linagliptin and 1500 mg metformin XR as 2 FDC tablets or the 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=55)[1]					
AUC_{0-72} [nmol·h/L]	307	299	102.8	(98.9, 106.8)	11.5
C_{max} [nmol/L]	9.46	8.91	106.2	(98.4, 114.6)	23.5
$AUC_{0-\infty}$ [nmol·h/L]	506	499	101.5	(95.7, 107.5)	17.5
Metformin (FDC N=53, free combination N=55)[2]					
AUC_{0-tz} [ng·h/mL]	10 627	10 415	102.0	(94.0, 110.7)	25.5
C_{max} [ng/mL]	1309	1245	105.1	(95.8, 115.3)	29.4
$AUC_{0-\infty}$ [ng·h/mL]	11 056	10 832	102.1	(94.2, 110.6)	25.0
Part 2 (fed conditions)					
Linagliptin (FDC N=14, free combination N=16)					
AUC_{0-72} [nmol·h/L]	262	258	101.5	(97.0, 106.1)	6.6
C_{max} [nmol/L]	7.18	6.73	106.7	(97.6, 116.7)	13.3
$AUC_{0-\infty}$ [nmol·h/L]	458	431	106.3	(100.3, 112.8)	8.7
Metformin (FDC N=15, free combination N=16)					
AUC_{0-tz} [ng·h/mL]	18 727	19 434	96.4	(90.0, 103.2)	10.7
C_{max} [ng/mL]	1739	1527	113.9	(108.7, 119.3)	7.2
$AUC_{0-\infty}$ [ng·h/mL]	19 073	19 707	96.8	(90.3, 103.7)	10.7

[1] C_{max} analysis linagliptin: N=53 for treatment with FDC, N=56 for treatment with free combination

[2] C_{max} analysis metformin: N=54 for treatment with FDC, N=56 for treatment with free combination

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Safety Results:

During the treatment periods of the 2 study parts, adverse events (AEs) were reported for a total of 54 subjects (73.0%). No deaths, no serious or severe AEs, no protocol-specified adverse events of special interest, or other significant AEs according to ICH E3 were reported in this study. All AEs were of mild or moderate intensity and had either resolved by the end of the study or were 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 26 subjects (46.4%) during the treatment period with the free combination and for 28 subjects (51.9%) during the treatment period with the FDC tablet. Twenty-two subjects (37.9%) reported AEs that were assessed as drug-related by the investigator (headache, dizziness, syncope, oropharyngeal pain, diarrhoea, abdominal pain, nausea, dry mouth, dyspepsia, salivary hypersecretion, pruritus, muscle spasms, and medication residue present). Adverse events reported with a frequency of >5% in this study part on the preferred term level were headache (18 subjects, 31.0%), dizziness, abdominal pain (reported for 6 subjects each, 10.3%), rhinitis, diarrhoea, back pain (reported for 4 subjects each, 6.9%), and fatigue (3 subjects, 5.2%). Two subjects discontinued the study prematurely due to non-serious AEs in Part1: one subject discontinued due to an accident and 1 subject due to gastroenteritis.

In Part 2, AEs were reported for 8 subjects (50.0%) during the treatment period with the free combination and for 3 subjects (18.8%) during the treatment period with the FDC tablet. Five subjects (31.3%) reported AEs that were assessed as drug-related by the investigator (headache, diarrhoea, rhinorrhea, abdominal discomfort). Adverse events reported in more than 1 subject in this study part on the preferred term level were headache (8 subjects, 50.0%), dizziness, and diarrhoea (reported for 2 subjects each, 12.5%).

Conclusions:

Two fixed-dose combination tablets each of 2.5 mg linagliptin/750 mg metformin XR were bioequivalent to 1 tablet 5 mg linagliptin and 3 tablets 500 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.