Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005144-28	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 1 of 6	
Report Date: 19 FEB 2015	**Trial No. / Doc. No.:** 1288.11 / c02728714-01	**Dates of Trial:** 24 Apr 2014 – 11 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/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 Site:	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: two 2.5 mg linagliptin/1000 mg metformin XR FDC tablets versus the free combination (1 tablet 5 mg linagliptin and 4 tablets 500 mg metformin XR) under fasted conditions Part 2: two 2.5 mg linagliptin/1000 mg metformin XR FDC tablets versus the free combination (1 tablet 5 mg linagliptin and 4 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 (for primary endpoints): 57 (linagliptin), 56 (metformin) Free combination: Treated: 56 Analysed (for primary endpoints): 55 (linagliptin), 56 (metformin)

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005144-28	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 2 of 6	
Report Date: 19 FEB 2015	**Trial No. / Doc. No.:** 1288.11 / c02728714-01	**Dates of Trial:** 24 Apr 2014 – 11 Jul 2014	**Date of Revision:** Not applicable

No. of Subjects (cont.):	Part 2 (fed conditions): FDC: Treated: 16 Analysed (for primary endpoints): 15 (both analytes) Free combination: Treated: 16 Analysed (for primary endpoints): 16 (linagliptin), 15 (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/1000 mg metformin XR FDC tablet
Dose:	5 mg linagliptin and 2000 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.:	B141000640 (3117868R)
Comparator Products:	Comparator product 1: Tradjenta® (5 mg linagliptin tablet) Comparator product 2: Glumetza® (500 mg metformin XR tablet)
Dose:	5 mg linagliptin and 2000 mg metformin XR (given as 1 tablet 5 mg linagliptin and 4 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 Nos.:	Tradjenta® 5 mg: B141000006 (361463C) Glumetza® 500 mg: B131003751 (MTBT9461)
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: monitoring of adverse events (AEs; including clinically relevant findings from the physical examination), safety laboratory tests, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG).

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005144-28	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 3 of 6	
Report Date: 19 FEB 2015	**Trial No. / Doc. No.:** 1288.11 / c02728714-01	**Dates of Trial:** 24 Apr 2014 – 11 Jul 2014	**Date of Revision:** Not applicable

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 subjects were entered into the study and treated, 58 in Part 1 (fasted conditions) and 16 in Part 2 (fed conditions). Seventy-two subjects completed the trial according to protocol, 56 in Part 1 and 16 in Part 2. Two subjects participating in Part 1 withdrew their consent and prematurely discontinued trial participation. Both subjects were treated with the FDC in the first treatment period but did not receive the free combination in the second treatment period. There were no important protocol violations in this trial.

Of the 58 subjects entered in Part 1, 20 (34.5%) were male and 38 (65.5%) were female. All subjects were White. The age (mean and standard deviation [SD]) of the subjects was 33.1 (9.8) years and the BMI (mean and SD) was 23.38 (2.71) kg/m^2.

Of the 16 subjects entered in Part 2, 9 (56.3%) were male and 7 (43.8%) were female. One subject was Black (6.3%); 15 subjects were White (93.8%). The age of the subjects was 32.6 (8.2) years and the BMI was 24.21 (2.10) kg/m^2.

Clinical Pharmacology Results:

In both study parts, geometric mean (gMean) plasma concentration-time profiles and pharmacokinetic parameters of linagliptin and metformin were similar for the FDC and the free combination.

The adjusted gMean values, the adjusted gMean ratios FDC/free combination, 2-sided 90% CIs, and intrasubject geometric coefficient of variation (gCV) values for all primary and secondary endpoints are summarised in Table 1 below. In both study parts, gMean ratios FDC/free combination for the primary endpoints AUC_{0-72} and C_{max} of linagliptin and AUC_{0-tz} and C_{max} of metformin and the corresponding 2-sided 90% CIs were

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005144-28	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 4 of 6	
Report Date: 19 FEB 2015	**Trial No. / Doc. No.:** 1288.11 / c02728714-01	**Dates of Trial:** 24 Apr 2014 – 11 Jul 2014	**Date of Revision:** Not applicable

Clinical Pharmacology Results (cont.):

within the pre-defined acceptance range of 80.00 to 125.00%. Thus, bioequivalence was established between the FDC and the free combination under fasted and fed conditions. For the secondary endpoints $AUC_{0-\infty}$ of linagliptin and $AUC_{0-\infty}$ of metformin, gMean ratios FDC/free combination and 2-sided 90% CIs were also within the acceptance range of 80.00 to 125.00% under fasted and fed conditions.

Table 1: Analysis of bioequivalence of linagliptin and metformin after administration of 5 mg linagliptin and 2000 mg metformin XR as 2 FDC tablets (2.5 mg/1000 mg) or the free combination under fasted and fed conditions

Analyte Parameter	Adjusted gMean FDC	Adjusted gMean free combination	Adjusted gMean ratio FDC/free combination [%]	Two-sided 90% CI (upper limit, lower limit) [%]	Intra-individual gCV [%]
Part 1 (fasted conditions)					
Linagliptin (FDC N=57, free combination N=55)					
AUC_{0-72} [nmol·h/L]	289	278	103.7	(100.7, 106.7)	9.1
C_{max} [nmol/L]	9.48	8.27	114.6	(107.7, 121.9)	19.6
$AUC_{0-\infty}$ [nmol·h/L]	474	458	103.5	(98.4, 108.8)	15.8
Metformin (FDC N=56[1], free combination N=56)					
AUC_{0-tz} [ng·h/mL]	11 601	12 028	96.5	(91.2, 102.0)	17.6
C_{max} [ng/mL]	1486	1517	98.0	(92.0, 104.3)	19.9
$AUC_{0-\infty}$ [ng·h/mL]	12 162	12 737	95.5	(89.7, 101.6)	19.7
Part 2 (fed conditions)					
Linagliptin (FDC N=15, free combination N=16)					
AUC_{0-72} [nmol·h/L]	269	265	101.6	(93.7, 110.2)	12.7
C_{max} [nmol/L]	6.61	6.73	98.3	(86.5, 111.6)	20.1
$AUC_{0-\infty}$ [nmol·h/L]	452	446	101.4	(91.1, 112.7)	16.7
Metformin (FDC N=15, free combination N=15)					
AUC_{0-tz} [ng·h/mL]	19 953	20 411	97.8	(90.5, 105.6)	11.7
C_{max} [ng/mL]	1663	1571	105.9	(96.7, 115.9)	13.8
$AUC_{0-\infty}$ [ng·h/mL]	20 346	20 721	98.2	(90.7, 106.3)	11.9

[1] C_{max}: N=57

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005144-28	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 5 of 6	
Report Date: 19 FEB 2015	**Trial No. / Doc. No.:** 1288.11 / c02728714-01	**Dates of Trial:** 24 Apr 2014 – 11 Jul 2014	**Date of Revision:** Not applicable

Safety Results:

No serious AEs, no protocol-specified AEs of special interest, and no other significant AEs according to ICH E3 occurred in this trial, and no subject discontinued the trial due to an AE. All subjects had recovered from their AEs by the end of the trial.

Safety laboratory tests and the evaluation of vital signs and ECG revealed no clinically significant findings in this trial.

Part 1 (fasted conditions)

Adverse events were reported for 39 subjects (67.2%). Twenty-eight subjects (50.0%) reported AEs in the treatment period with the free combination and 26 subjects (44.8%) reported AEs in the treatment period with the FDC. Adverse events reported for more than 1 subject were headache (16 subjects, 27.6%), diarrhoea (8 subjects, 13.8%), abdominal pain (7 subjects, 12.1%), nausea (6 subjects, 10.3%), dizziness (5 subjects, 8.6%), abdominal discomfort (4 subjects, 6.9%), nasopharyngitis (3 subjects, 5.2%), vessel puncture site haematoma (3 subjects, 5.2%), and otitis externa (2 subjects, 3.4%). Twenty-seven subjects (46.6%) reported AEs that were assessed by the investigator as drug-related. The most frequent drug-related AEs were gastrointestinal disorders (17 subjects, 29.3%). One subject reported an AE of severe intensity (headache) in the treatment period with the FDC; all other AEs were of mild or moderate intensity.

Part 2 (fed conditions)

Adverse events were reported for 10 subjects (62.5%). Eight subjects (50.0%) reported AEs in the treatment period with the free combination and 5 subjects (31.3%) reported AEs in the treatment period with the FDC. Adverse events reported for more than 1 subject were diarrhoea (5 subjects, 31.3%), headache (4 subjects, 25.0%), abdominal pain, nausea, and vomiting (each reported for 2 subjects, 12.5%). Seven subjects (43.8%) reported AEs that were assessed by the investigator as drug-related. The most frequent drug-related AEs were gastrointestinal disorders (6 subjects, 37.5%). All AEs in this study part were of mild or moderate intensity.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005144-28	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 6 of 6	
Report Date: 19 FEB 2015	**Trial No. / Doc. No.:** 1288.11 / c02728714-01	**Dates of Trial:** 24 Apr 2014 – 11 Jul 2014	**Date of Revision:** Not applicable

Conclusions:

Bioequivalence under fasted and fed conditions was established between two 2.5 mg linagliptin/1000 mg metformin XR FDC tablets and the free combination of 1 tablet 5 mg linagliptin and 4 tablets 500 mg metformin XR. For both linagliptin and metformin, the 90% confidence intervals of the ratios of the geometric means for each of the primary endpoints were contained in the pre-defined acceptance range of 80.00 to 125.00%.

The treatments investigated in this trial were well tolerated when administered to healthy male and female subjects.