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.

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**.

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| **Name of company:** Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:** Not applicable | | **EudraCT No.:** Not applicable | |
| **Name of active ingredient:** Linagliptin, metformin XR | | **Page:** 1 of 6 | |
| **Report date:** 22 APR 2014 | **Trial No. / Doc No.:** 1288.8 / c02162111-02 | **Dates of trial:** 02 MAY 2013 – 19 AUG 2013 | **Date of revision:** Not applicable |



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| **Title of trial:** | Relative bioavailability of two newly developed extended release FDC tablet strengths (5 mg/1000 mg and 2.5 mg/750 mg) of linagliptin/metformin extended release compared with the free combination of linagliptin and metformin extended release in healthy subjects (an open-label, randomised, single dose, two-way crossover study) |
| **Principal Investigator:** | [redacted] MD, PhD |
| **Trial site:** | [redacted] USA |
| **Publication (reference):** | Data from this trial have not been published. |
| **Clinical phase:** | I |
| **Objectives:** | The objective was to investigate the relative bioavailability of linagliptin / metformin extended release (XR) fixed dose combination (FDC) tablets versus the free combination of linagliptin tablets and metformin XR tablets. |
| **Methodology:** | Randomised, open-label, single-dose, 2-way crossover trial with 3 individual study parts:<br>a) 5 mg linagliptin / 1000 mg metformin XR under fasted conditions: FDC versus free combination<br>b) 5 mg linagliptin / 1000 mg metformin XR under fed conditions: FDC versus free combination<br>c) 5 mg linagliptin / 1500 mg metformin XR under fasted conditions: FDC versus free combination |
| **No. of subjects:** | |
| **planned:** | to be entered: 72 (24 in each study part) |
| **actual:** | entered: 72 (24 in each study part)<br>a) 5 mg linagliptin / 1000 mg metformin XR fasted<br>FDC: treated: 23 analysed (for primary endpoints): 23<br>Free combination: treated: 23 analysed (for primary endpoints): 23<br>b) 5 mg linagliptin / 1000 mg metformin XR fed<br>FDC: treated: 22 analysed (for primary endpoints): 22<br>Free combination: treated: 23 analysed (for primary endpoints): 22 (linagliptin), 23 (metformin) |

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| | c) 5 mg linagliptin / 1500 mg metformin XR fasted<br>FDC: treated: 23 analysed (for primary endpoints): 21<br>Free combination: treated: 23 analysed (for primary endpoints): 22 |
| **Diagnosis and main criteria for inclusion:** | Healthy male and female subjects, age 18 to 50 years, body mass index (BMI) 18.5 to 29.9 kg/m$^2$ |
| **Test products:** | Test product 1: 5 mg linagliptin / 1000 mg metformin XR FDC tablet<br>Test product 2: 2.5 mg linagliptin / 750 mg metformin XR FDC tablet<br>The FDC tablet consisted of an extended release metformin tablet with an immediate release linagliptin coat covering the metformin tablet. |
| **dose:** | a) 5 mg linagliptin / 1000 mg metformin XR<br>b) 5 mg linagliptin / 1000 mg metformin XR<br>c) 5 mg linagliptin / 1500 mg metformin XR (given as two 2.5 mg linagliptin / 750 mg metformin XR FDC tablets) |
| **mode of admin.:** | Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study parts and after a high-fat, high-calorie meal for the fed study part |
| **batch no.:** | 3108478R (5 mg linagliptin / 1000 mg metformin XR FDC)<br>3108477R (2.5 mg linagliptin / 750 mg metformin XR FDC) |
| **Reference products:** | Reference product 1: Tradjenta® 5 mg immediate release tablet<br>Reference product 2: Glumetza® 500 mg extended release tablet |
| **dose:** | a) 5 mg linagliptin and 1000 mg metformin XR (given as two 500 mg tablets)<br>b) 5 mg linagliptin and 1000 mg metformin XR (given as two 500 mg tablets)<br>c) 5 mg linagliptin and 1500 mg metformin XR (given as three 500 mg tablets) |
| **mode of admin.:** | Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study parts and after a high-fat, high-calorie meal for the fed study part |
| **batch no.:** | 260643B (Tradjenta® 5 mg)<br>MTBT5761 (Glumetza® 500 mg) |
| **Duration of treatment:** | Single dose in each treatment period separated by a washout phase of at least 35 days |

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**Criteria for evaluation:**

**Clinical pharmacology:** Primary endpoints: $AUC_{0-72}$ and $C_{max}$ (linagliptin), $AUC_{0-tz}$ and $C_{max}$ (metformin)
Secondary endpoint: $AUC_{0-\infty}$ (linagliptin and metformin)

**Safety:** Adverse events (AEs), safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse rate), and physical examination (occurrence of findings)

**Statistical methods:** Relative bioavailability was estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their 2-sided 90% confidence intervals (CIs) were provided. The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs were calculated based on the residual error from ANOVA.
Descriptive statistics were calculated for all endpoints.

**SUMMARY – CONCLUSIONS:**

**Clinical pharmacology results:** A total of 72 healthy subjects were entered into the study and treated, 24 in each study part. Forty-two subjects (58.3%) were male and 30 subjects (41.7%) were female. Two subjects (2.8%) were Asian, 16 subjects (22.2%) were black, and 54 subjects (75.0%) were white. The age (mean and standard deviation [SD]) of the treated subjects was 31.3 (8.8) years and the BMI (mean and SD) was 25.21 (2.74) $kg/m^2$. Of the 72 treated subjects, 65 subjects completed the trial according to protocol, whereas 7 subjects prematurely discontinued trial participation: 1 subject discontinued due to an AE, 2 subjects were removed from the study due to non-compliance with the protocol, 3 subjects were lost to follow-up, and 1 subject discontinued due to other reasons. Two subjects were reported with important protocol violations (positive alcohol test, positive urine drug screen) and were removed from the study due to non-compliance.

For each study part, 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 to 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. For each study part, the adjusted gMean ratios FDC to free combination for $AUC_{0-72}$ and $C_{max}$ of linagliptin and $AUC_{0-tz}$ and $C_{max}$ of metformin were close to 100%.

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**Clinical pharmacology results (continued):**

Table 1: Analysis of relative bioavailability of linagliptin and metformin after administration of linagliptin and 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 [%] |
|---|---|---|---|---|---|
| *Study part a) 5 mg linagliptin / 1000 mg metformin XR fasted* | | | | | |
| Linagliptin (FDC N=23, free combination N=23) | | | | | |
| $AUC_{0-72}$ [nmol·h/L] | 317.0 | 319.2 | 99.3 | (95.3, 103.5) | 8.0 |
| $C_{max}$ [nmol/L] | 10.1 | 10.6 | 94.9 | (86.8, 103.6) | 17.1 |
| $AUC_{0-\infty}$ [nmol·h/L] | 546.1 | 526.5 | 103.7 | (97.1, 110.8) | 12.8 |
| Metformin (FDC N=23, free combination N=23) | | | | | |
| $AUC_{0-tz}$ [ng·h/mL] | 8629.0 | 8913.7 | 96.8 | (86.6, 108.2) | 21.8 |
| $C_{max}$ [ng/mL] | 1047.4 | 1085.6 | 96.5 | (84.8, 109.8) | 25.5 |
| $AUC_{0-\infty}$ [ng·h/mL] | 9037.6 | 9326.5 | 96.9 | (86.8, 108.2) | 21.5 |
| *Study part b) 5 mg linagliptin / 1000 mg metformin XR fed* | | | | | |
| Linagliptin (FDC N=22, free combination N=22)[1] | | | | | |
| $AUC_{0-72}$ [nmol·h/L] | 309.6 | 304.9 | 101.5 | (98.4, 104.7) | 5.5 |
| $C_{max}$ [nmol/L] | 7.7 | 7.9 | 96.8 | (90.2, 103.8) | 13.0 |
| $AUC_{0-\infty}$ [nmol·h/L] | 537.1 | 510.0 | 105.3 | (99.9, 111.0) | 9.6 |
| Metformin (FDC N=22, free combination N=23) | | | | | |
| $AUC_{0-tz}$ [ng·h/mL] | 13772.0 | 13851.1 | 99.4 | (95.6, 103.4) | 7.4 |
| $C_{max}$ [ng/mL] | 1119.0 | 1084.5 | 103.2 | (98.9, 107.7) | 8.1 |
| $AUC_{0-\infty}$ [ng·h/mL] | 14031.3 | 14069.7 | 99.7 | (96.1, 103.5) | 7.0 |
| *Study part c) 5 mg linagliptin / 1500 mg metformin XR fasted* | | | | | |
| Linagliptin (FDC N=21, free combination N=22) | | | | | |
| $AUC_{0-72}$ [nmol·h/L] | 325.8 | 322.9 | 100.9 | (98.2, 103.7) | 5.1 |
| $C_{max}$ [nmol/L] | 11.6 | 10.7 | 108.6 | (99.5, 118.5) | 16.5 |
| $AUC_{0-\infty}$ [nmol·h/L] | 562.9 | 581.1 | 96.9 | (90.2, 104.1) | 13.5 |
| Metformin (FDC N=21, free combination N=22) | | | | | |
| $AUC_{0-tz}$ [ng·h/mL] | 10472.9 | 10543.5 | 99.3 | (90.1, 109.5) | 18.5 |
| $C_{max}$ [ng/mL] | 1347.0 | 1250.6 | 107.7 | (92.5, 125.4) | 29.3 |
| $AUC_{0-\infty}$ [ng·h/mL] | 11037.7 | 11512.2 | 95.9 | (86.7, 106.0) | 19.1 |

[1] One subject excluded from $AUC_{0-72}$ calculation (FDC N=21, free combination N=21)

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**Safety results:**

In study part a), 22 subjects were administered 2 doses of 5 mg linagliptin and 1000 mg metformin XR in the fasted state, while 2 subjects only received the first dose of trial medication. In study part b), 21 subjects were administered 2 doses of 5 mg linagliptin and 1000 mg metformin XR in the fed state, while 3 subjects only received the first dose of trial medication. In study part c), 22 subjects were administered 2 doses of 5 mg linagliptin and 1500 mg metformin XR in the fasted state, while 2 subjects only received the first dose of trial medication.

Adverse events were reported for a total of 20 subjects (27.8%) in this study. The most frequently reported AEs overall were headache (5 subjects, 6.9%) and dizziness (3 subjects, 4.2%). For 1 subject an SAE (road traffic accident) was reported, which was not assessed as drug-related. It was the only AE of severe intensity; all other AEs were of mild or moderate intensity. No protocol-specified significant AEs or other significant AEs according to ICH E3 were reported. One subject discontinued the trial due to an AE (influenza-like illness). A total of 11 subjects (15.3%) reported AEs that were assessed by the investigator as drug-related.

In study part a), 2 subjects (8.7%) reported AEs during the treatment period with the free combination and 6 subjects (26.1%) reported AEs during the treatment period with the FDC tablet. Four subjects (16.7%) reported AEs that were assessed by the investigator as drug-related (headache in 2 subjects, dizziness, back pain, and myalgia).

In study part b), 4 subjects (17.4%) reported AEs during the treatment period with the free combination and 3 subjects (13.6%) reported AEs during the treatment period with the FDC tablet. Three subjects (12.5%) reported AEs that were assessed as drug-related (decreased appetite, dizziness, dysgeusia, and fatigue).

In study part c), 5 subjects (21.7%) reported AEs during the treatment period with the free combination and 4 subjects (17.4%) reported AEs during the treatment period with the FDC tablets. Four subjects (16.7%) reported AEs that were assessed as drug-related (headache in 2 subjects, nausea in 2 subjects, vomiting in 2 subjects, decreased appetite, dizziness, and hiccups).

There were no clinically relevant findings with respect to safety laboratory tests, vital signs, or ECG.

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**Conclusions:** The relative bioavailability of linagliptin/metformin XR FDC tablets versus the free combination of linagliptin tablets and metformin XR tablets was investigated for 2 FDC tablet strengths (5 mg/1000 mg and 2.5 mg/750 mg) under fed conditions (for the 5 mg/1000 mg tablet strength) and fasted conditions (for both tablet strengths). All adjusted gMean ratios FDC to free combination for $AUC_{0-72}$ and $C_{max}$ of linagliptin and $AUC_{0-tz}$ and $C_{max}$ of metformin were close to 100%. All treatments investigated in this trial were safe and well tolerated in healthy volunteers.