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***.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-015677-13	
Name of active ingredients: Linagliptin, metformin		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 AUG 2010	**Trial No. / U No.:** 1288.3 / U10-2303-01	**Dates of trial:** 14 JAN 2010 – 26 APR 2010	**Date of revision:** Not applicable

Title of trial:	Bioequivalence of a 2.5 mg linagliptin / 850 mg metformin fixed dose combination tablet compared with single linagliptin 2.5 mg and metformin 850 mg tablets administered together in healthy male and female volunteers (an open-label, randomised, single-dose, two-way crossover, Phase I trial)
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre of Boehringer Ingelheim, Biberach, Germany
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	To demonstrate bioequivalence of a 2.5 mg linagliptin / 850 mg metformin fixed dose combination (FDC) tablet compared to single tablets of linagliptin 2.5 mg and metformin 850 mg administered together
Methodology:	Open-label, randomised, single-dose, 2-way crossover design
No. of subjects:	
planned:	entered: 96
actual:	entered: 96
	Treatment A (FDC tablet): treated: 96 analysed (for primary endpoints): 95
	Treatment B (single tablets): treated: 96 analysed (for primary endpoints): 94 (linagliptin), 93 (metformin)
Diagnosis and main criteria for inclusion:	Healthy volunteers, male and female, age 18 to 55 years, body mass index (BMI) range: 18.5 to 29.9 kg/m^2
Test product:	Linagliptin/metformin FDC tablet
dose:	2.5 mg linagliptin and 850 mg metformin
mode of admin.:	Peroral with 240 mL water in a standing position after an overnight fast of at least 10 h
batch no.:	902831

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Reference therapy:	Linagliptin tablet and metformin (Glucophage®) tablet
dose:	2.5 mg linagliptin and 850 mg metformin
mode of admin.:	Peroral with 240 mL water in a standing position after an overnight fast of at least 10 h
batch no.:	Linagliptin: B081004241, metformin: X1486 (Merck Pharma GmbH)
Duration of treatment:	Single dose in each treatment period separated by a wash-out phase of at least 35 days
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints: AUC_{0-72} and C_{max} for linagliptin; $AUC_{0-\infty}$ and C_{max} for metformin Secondary endpoints: $AUC_{0-\infty}$ for linagliptin; AUC_{0-tz}, $\%AUC_{tz-\infty}$, AUC_{t1-t2}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F for both analytes
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), laboratory tests, adverse events (AEs), tolerability assessment
Statistical methods:	Primary endpoints and key secondary endpoints: point estimators (geometric means [gMean]) of the median intra-subject ratios and their 2-sided 90% confidence intervals (CIs). Statistical model: analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. Confidence intervals were based on the residual error from ANOVA. Other parameters: descriptive statistics and tabulated frequencies.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

The study population consisted of 96 healthy volunteers, 42 male and 54 female. All subjects were White and aged between 19 and 55 years (mean: 37.1 years, standard deviation [SD]: 9.8 years) with a BMI of 18.6 to 28.7 kg/m^2 (mean: 23.66 kg/m^2, SD: 2.88 kg/m^2). No relevant medical history or baseline conditions were reported for any of the participating subjects. All subjects completed the 2 treatment periods and the end-of-study examination. One important protocol violation was reported in this trial: 1 subject did not swallow the single linagliptin tablet by mistake.

For both linagliptin and metformin, gMean plasma concentration-time profiles were similar for the FDC and single tablet treatments.

Geometric mean AUC_{0-72} of linagliptin was 159 nmol·h/L for the FDC and 154 nmol·h/L for the single tablets (the inter-subject geometric coefficient of variation [gCV]) was 27.2% and 30.4%, respectively). Geometric mean C_{max} of linagliptin was 5.23 nmol/L (gCV 24.1%) for the FDC and 4.96 nmol/L (gCV 24.5%) for the single tablets. Median t_{max} was 3.00 h for both the FDC and the single tablets.

Geometric mean $AUC_{0-\infty}$ of metformin was 11400 ng·h/mL (gCV 25.3%) for the FDC and 11300 ng·h/mL (gCV 25.9%) for the single tablets. Geometric mean AUC_{0-tz} of metformin was 11100 ng·h/mL (gCV 25.6%) for the FDC and 11000 ng·h/mL (gCV 26.4%) for the single tablets. Geometric mean C_{max} of metformin was 1650 ng/mL (gCV 26.6%) for the FDC and 1670 ng/mL (gCV 28.5%) for the single tablets. Median t_{max} was 3.00 h for both the FDC and the single tablets.

The adjusted gMean ratios (FDC to single tablets), 90% CIs, and intra-subject gCVs of AUC_{0-72} (linagliptin only), $AUC_{0-\infty}$ and AUC_{0-tz} (metformin only), and C_{max} (both analytes) are summarised in Table 1.

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Clinical pharmacology results (continued):

Table 1: Adjusted gMean ratio, 90% confidence interval and intra-subject gCV for the key parameters of linagliptin and metformin

	Adjusted gMean ratio (FDC/single tablets[1]) [%]	2-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Linagliptin 2.5 mg				
AUC_{0-72}	104.0	100.2	108.0	15.4
C_{max}	105.9	102.7	109.3	12.9
Metformin 850 mg				
$AUC_{0-\infty}$	101.2	98.3	104.1	11.8
AUC_{0-tz}	100.8	98.0	103.8	11.9
C_{max}	99.8	96.2	103.6	15.4

[1] FDC: N=95; single tablets: N=94 (linagliptin), N=93 (metformin)

For both linagliptin and metformin, all 90% CIs for AUC and C_{max} were contained in the bioequivalence acceptance range of 80 to 125%. Therefore, bioequivalence of the FDC compared to the single tablets can be concluded.

Safety results:

All 96 subjects were administered a total dose of 5 mg linagliptin and a total dose of 1700 mg metformin during the trial. The subject who did not swallow the linagliptin tablet was also defined as exposed to linagliptin.

Forty-four subjects (45.8%) reported at least 1 AE during the 2 treatment periods. Twenty-nine subjects (30.2%) experienced AEs during the treatment period with single tablets of linagliptin and metformin and 25 subjects (26.0%) experienced AEs during the treatment period with the FDC. Overall, the most frequently reported AEs by system organ class were nervous system disorders (20 subjects, 20.8%), gastrointestinal disorders (20 subjects, 20.8%), and infections and infestations (12 subjects, 12.5%). On the preferred term level, the most frequently reported AEs were headache (17 subjects, 17.7%), nasopharyngitis (12 subjects, 12.5%), diarrhoea (7 subjects, 7.3%), nausea (6 subjects, 6.3%), and vomiting (6 subjects, 6.3%).

Four subjects (4.2%) experienced AEs of severe intensity: 1 subject experienced severe vomiting in both treatment periods, 2 subjects experienced severe

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headache and 1 subject experienced severe back pain in the treatment period with the single tablets. Except for back pain, all AEs of severe intensity were considered drug-related.

Thirty-three subjects (34.4%) experienced AEs that were assessed as drug-related by the investigator: headache (single tablets: 10 subjects/ FDC: 9 subjects), dizziness (2/0 subjects), diarrhoea (5/3 subjects), nausea (3/3 subjects), vomiting (5/2 subjects), abdominal pain upper (2/1 subjects), and dyspepsia (1/0 subject).

There was no serious AE (SAE) reported in this trial and no subject was discontinued due to an AE.

Clinical laboratory tests, vital signs and ECG recordings revealed no safety concerns in this study. Global tolerability was assessed as good for the majority of subjects in both treatment periods (single tablets 85.4%, FDC 92.7%). In a few subjects global tolerability was assessed as satisfactory (single tablets 7.3%, FDC 4.2%) or not satisfactory (single tablets 7.3%, FDC 3.1%).

Conclusions:

The fixed dose combination tablet of linagliptin 2.5 mg and metformin 850 mg was bioequivalent to single tablets of 2.5 mg linagliptin and 850 mg metformin administered together. Both the fixed dose combination and combined administration as single tablets were well tolerated in the majority of healthy male and female subjects and there were no safety concerns.