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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-015655-24	
Names of active ingredients: Linagliptin, metformin		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 AUG 2010	**Trial No. / U No.:** 1288.1 / U10-2278-02	**Dates of trial:** 11 JAN 2010 - 21 APR 2010	**Date of revision:** 29 MAR 2011

Title of trial:	Bioequivalence of a 2.5 mg linagliptin / 1000 mg metformin fixed-dose combination tablet compared with single linagliptin 2.5 mg and metformin 1000 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 Pharma GmbH & Co. KG, 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/1000 mg metformin fixed-dose combination (FDC) tablet compared with single tablets of linagliptin 2.5 mg and metformin 1000 mg administered together.
Methodology:	Open-label, randomised, single-dose, 2-way crossover design
No. of subjects:	
planned:	entered: 96
actual:	Treatment A (FDC tablet): entered: 96 treated: 96 analysed (for primary endpoints): 96 Treatment B (single tablets): entered: 96 treated: 95 analysed (for primary endpoints): 93
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 1000 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.:	903235

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Reference therapy:	Linagliptin tablet and metformin (Glucophage®) tablet
dose:	2.5 mg linagliptin and 1000 mg metformin
mode of admin.:	Peroral with 240 mL of water in a standing position after an overnight fast of at least 10 h
batch no.:	Linagliptin: B081004241 Metformin: X1444 Merck Pharma GmbH
Duration of treatment:	Single dose in each treatment period separated by a washout 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) of the median intrasubject 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. All other parameters: descriptive statistics and tabulated frequencies.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

A total of 96 healthy volunteers participated in the study, 62 male (64.6%) and 34 female (35.4%). Ninety-five subjects were white, 1 subject was black/African American. Age ranged from 18 to 54 years (mean: 35.2 years, SD: 10.7 years), and BMI ranged from 18.9 to 29.7 kg/m^2 (mean: 24.32 kg/m^2, SD: 2.66 kg/m^2). No relevant medical history or baseline conditions were reported for any of the participating subjects.

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

Geometric mean AUC_{0-72} of linagliptin (intersubject geometric coefficient of variation, gCV) was 157 nmol·h/L (29.5%) for the FDC and 147 nmol·h/L (27.9%) for the single tablets. Geometric mean C_{max} was 5.05 nmol/L (gCV 25.7%) for FDC and 4.88 nmol/L (gCV 25.7%) for the single tablets. Median t_{max} was 3.00 h for both the FDC and single tablets.

Geometric mean $AUC_{0-\infty}$ of metformin (intersubject gCV%) was 11100 ng·h/mL (25.7%) for the FDC and 10700 ng·h/mL (25.9%) for the single tablets. Geometric mean AUC_{0-tz} of metformin (gCV%) was 10900 ng·h/mL (26.4%) for the FDC and 10400 ng·h/mL (26.3%) for the single tablets. Geometric mean C_{max} was 1680 ng/mL (gCV 27.1%) for the FDC and 1600 ng/mL (gCV 28.1%) for the single tablets. Median t_{max} was 2.51 h for the FDC and 3.00 h for the single tablets.

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Clinical pharmacology results (continued):

Adjusted geometric mean ratios (FDC/single tablets), 90% CIs and intrasubject gCVs of AUC_{0-72} (linagliptin only), $AUC_{0-\infty}$ and AUC_{0-tz} (metformin only), and C_{max} are summarised in Table 1 below.

Table 1: Adjusted geometric mean ratio, 90% confidence interval and intrasubject gCV for the pharmacokinetic parameters of linagliptin and meformin relevant for the assessment of bioequivalence

	Adjusted geometric mean ratio (%) FDC/single tablets FDC N=96 single tablets N=93	2-sided 90% confidence interval		Intrasubject gCV (%)
		Lower limit (%)	Upper limit (%)	
Linagliptin 2.5 mg				
AUC_{0-72}	106.5	102.8	110.3	14.5
C_{max}	103.4	100.3	106.7	12.7
Metformin 1000 mg				
$AUC_{0-\infty}$	103.8	100.2	107.4	14.3
AUC_{0-tz}	103.9	100.3	107.7	14.6
C_{max}	104.6	100.1	109.2	17.9

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

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Safety results:	Administration of a 2.5 mg linagliptin/1000 mg metformin fixed dose combination tablet had no differential effect on the frequency or intensity of adverse events compared with single tablets of linagliptin 2.5 mg and metformin 1000 mg administered together. In total, 53 subjects (55.2%) reported at least 1 AE during the 2 treatment periods. Twenty-two subjects (22.9%) reported study drug-related AEs, as assessed by the Investigator. No deaths or other significant AEs were reported. Subject [redacted] was reported with a serious AE (ureteric calculus) during the washout period after FDC treatment and was excluded from second treatment period; the AE was assessed as not study drug-related by the investigator. All but 3 AEs were recovered until the end of the trial; follow-up was considered sufficient by the investigator. The most frequently reported AEs by MedDRA system organ class were gastrointestinal disorders (29.2% of the subjects), nervous system disorders (21.9%) and infections and infestations (15.6%). On the MedDRA preferred term level, the most frequently reported AEs were headache (18.8% of the subjects), diarrhoea, (17.7%) and nasopharyngitis (10.4%). Most AEs were of mild or moderate intensity, while 7 subjects (7.3%) were reported with severe AEs. Clinical laboratory tests and the evaluation of vital signs revealed no safety concerns. ECG examination of 1 subject showed a transient prolongation of the PQ interval reported as a mild AE.
Conclusions:	The fixed-dose combination tablet of linagliptin 2.5 mg and metformin 1000 mg was bioequivalent to single tablets of 2.5 mg linagliptin and 1000 mg metformin administered together. Both the fixed-dose combination and combined administration as single tablets were well tolerated and safe in healthy volunteers.