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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-019291-75	
Name of active ingredients: Linagliptin, metformin		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1288.6 / U11-1379-01	**Dates of trial:** 27 SEP 2010 – 02 DEC 2010	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of two different batches of a 2.5 mg linagliptin / 1000 mg metformin fixed dose combination tablet (FDC) 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, Ingelheim, Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of two different batches of a 2.5 mg linagliptin/1000 mg metformin fixed dose combination tablet
Methodology:	Open-label, randomised, 2-way crossover design
No. of subjects:	
planned:	entered: 40
actual:	entered: 40
	FDC tablet from the standard batch: entered: 40 treated: 40 analysed (for primary endpoints): 40
	FDC tablet from the side batch: entered: 40 treated: 40 analysed (for primary endpoints): 40
Diagnosis and main criteria for inclusion:	Healthy volunteers, male and female, age 21 to 50 years, body mass index (BMI) range: 18.5 to 29.9 kg/m^2
Test product:	Linagliptin/metformin FDC tablet (standard batch)
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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Module:		**Volume:**	
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Reference therapy:	Linagliptin/metformin FDC tablet (side batch)
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.:	B101002992
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-tz} and C_{max} for metformin Secondary endpoints: AUC_{0-tz} for linagliptin; $AUC_{0-\infty}$, t_{max}, λ_z, $t_{1/2}$, $\%AUC_{tz-\infty}$, MRT_{po}, CL/F, and V_z/F for both analytes
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, adverse events (AEs), tolerability assessment
Statistical methods:	Primary endpoints and key secondary endpoints: point estimators (geometric means [gMean]) 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 within sequences', 'period', and 'treatment'. Confidence intervals were based on the t-distribution. Other parameters: descriptive statistics and tabulated frequencies

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Module:		**Volume:**	
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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

The study population comprised 40 healthy volunteers, 20 male and 20 female. Thirty-nine subjects were white and 1 subject was Black or African American. Age ranged from 26 to 48 years (mean: 36.8 years, standard deviation [SD]: 6.8 years) and BMI ranged from 19.9 to 29.6 kg/m^2 (mean: 23.74 kg/m^2, SD: 2.74 kg/m^2). No relevant medical history or baseline conditions were reported for any of the participating subjects. All subjects completed both treatment periods. No important protocol violations were reported in this trial.

For both linagliptin and metformin, gMean plasma concentration-time profiles were similar for the FDC standard batch and side batch treatments.

Geometric mean AUC_{0-72} of linagliptin was 179 nmol·h/L for both the standard batch and side batch tablets (the intersubject geometric coefficient of variation [gCV]) was 21.6% for the standard batch tablets and 20.5% for the side batch tablets). Geometric mean C_{max} of linagliptin was 5.36 nmol/L (gCV 20.3%) for the standard batch tablets and 5.39 nmol/L (gCV 20.3%) for the side batch tablets. Median t_{max} was 3.00 h for both the standard batch and the side batch tablets.

Geometric mean AUC_{0-tz} of metformin was 12100 ng·h/mL for both the standard batch and side batch tablets (gCV 21.4% for the standard batch tablets and 19.4% for the side batch tablets). Geometric mean C_{max} of metformin was 1790 ng/mL (gCV 23.0%) for the standard batch tablets and 1820 ng/mL (gCV 25.5%) for the side batch tablets. Median t_{max} was 1.99 h for the standard batch tablets and 2.00 h for the side batch tablets.

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

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Name of active ingredients: Linagliptin, metformin		**Page:** 4 of 5	**Synopsis No.:**
Module:		**Volume:**	
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Clinical pharmacology results (continued):

Table 1: Adjusted gMean ratio, 90% confidence interval and intrasubject gCV for the key parameters of linagliptin and metformin (N=40)

	Adjusted gMean ratio (test/reference) [%]	2-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Linagliptin 2.5 mg				
AUC_{0-72}	100.1	96.1	104.2	10.9
$AUC_{0-\infty}$	100.1	94.7	105.8	14.8
C_{max}	99.4	94.2	105.0	14.5
Metformin 1000 mg				
AUC_{0-tz}	100.4	95.7	105.4	12.9
$AUC_{0-\infty}$	100.3	95.7	105.2	12.7
C_{max}	97.9	92.5	103.7	15.3

For both linagliptin and metformin, all 90% CIs for AUC and C_{max} were within the bioequivalence acceptance range of 80 to 125%.

Safety results:

Forty subjects received, as planned, a total dose of 5 mg linagliptin and a total dose of 2000 mg metformin during the trial.

Seventeen subjects (42.5%) experienced at least 1 AE during the 2 treatment periods. Ten subjects (25.0%) experienced AEs during the treatment period with the standard batch tablets and 12 subjects (30.0%) experienced AEs during the treatment period with the side batch tablets. The AEs with the highest incidences by system organ class were nervous system disorders (14 subjects, 35.0%), gastrointestinal disorders (4 subjects, 10.0%), and infections and infestations (3 subjects, 7.5%). On the preferred term level, the AEs with the highest incidences were headache (14 subjects, 35.0%), vomiting (3 subjects, 7.5%), and nasopharyngitis (3 subjects, 7.5%). Fourteen subjects (35.0%) had AEs that were assessed by the investigator as drug-related, the most frequent of which was headache (12 subjects). All AEs were of mild or moderate intensity.

All reported AE episodes had resolved by the end of the trial. No subject was discontinued due to an AE. No serious AEs (SAEs) or other significant AEs (according to ICH E3) were reported in this trial.

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Safety results (continued):	Clinical laboratory tests, vital signs, and ECG recordings revealed no safety concerns in this study. Global tolerability was assessed as 'good' for both treatment periods in 39 of the 40 exposed subjects and as 'not satisfactory' for one subject after treatment with the standard batch tablet. This assessment was based on AEs (headache of mild intensity and vomiting of moderate intensity) experienced by the subject.
Conclusions:	Bioequivalence was demonstrated between linagliptin/metformin FDC tablets with normal (standard batch) and slower (side batch) dissolution characteristics. For both linagliptin and metformin, the confidence limits of all pharmacokinetic parameters were well within the bioequivalence acceptance limits of 80% to 125%. Tablets from both batches were safe and well tolerated in healthy volunteers.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for secondary endpoints of the trial. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
Pharmacokinetic parameters (gMeans) of linagliptin	Table 15.6.3: 1
Pharmacokinetic parameters (gMeans) of metformin	Table 15.6.3: 4

Table 15.6.3: 1 Comparison of pharmacokinetic parameters (N, gMean and gCV [%]) of linagliptin by treatment

	FDC (side batch)(R)			FDC (standard batch)(T)		
	N	gMean	gCV [%]	N	gMean	gCV [%]
AUC_{0-72} [nmol*h/L]	40	179	20.5	40	179	21.6
C_{max} [nmol/L]	40	5.39	20.3	40	5.36	20.3
$t_{½}$ [h]	40	45.6	21.6	40	45.4	17.1
MRT_{po} [h]	40	64.5	19.5	40	64.6	15.7
CL/F [mL/min]	40	330	23.6	40	330	25.4
V_z/F [L]	40	1300	24.6	40	1300	22.8

Table 15.6.3: 4 Comparison of pharmacokinetic parameters (N, gMean and gCV [%]) of metformin by treatment

	FDC (side batch)(R)			FDC (standard batch)(T)		
	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0-\infty}$ [ng*h/mL]	40	12300	19.9	40	12400	21.2
$\%AUC_{tz-\infty}$ [%]	40	1.52	97.0	40	1.51	87.4
$AUC_{0-\infty}$ [ng*h/mL]	40	12300	19.9	40	12400	21.2
$\%AUC_{tz-\infty}$ [%]	40	1.43	98.8	40	1.45	87.5
AUC_{0-tz} [ng*h/mL]	40	12100	19.4	40	12100	21.4
C_{max} [ng/mL]	40	1820	25.5	40	1790	23.0
$t_{½}$ [h]	40	13.5	84.3	40	14.1	71.0
MRT_{po} [h]	40	8.23	36.9	40	8.27	31.1
CL/F [mL/min]	40	1350	19.9	40	1350	21.2
V_z/F [L]	40	1580	82.4	40	1640	74.3

1st and 2nd row: AUC extrapolation to infinite time and percentage of extrapolated area based on observed value of last data point
3rd and 4th row: AUC extrapolation to infinite time and percentage of extrapolated area based on predicted value of last data point

Source data: Section 15.6, Table 2.1: 3, 2.1: 4 pk\pkover.sas 05APR2011