Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.:** 2011-005423-41	
Name of active ingredient: Linagliptin (BI 1356), metformin		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 SEP 2012	**Trial No. / U No.:** 1288.20 / U12-2225-01	**Dates of trial:** 23 APR 2012 – 20 JUN 2012	**Date of revision:** Not applicable

Title of trial:	Bioequivalence of metformin under fed conditions after administration of a 2.5 mg linagliptin / 500 mg metformin fixed-dose-combination tablet compared with single linagliptin 2.5 mg and metformin 500 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 sites:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Birkendorfer Str. 65, Biberach/Riss, Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objectives:	The objective of the trial was to demonstrate bioequivalence of metformin under fed conditions after administration of a 2.5 mg linagliptin/500 mg metformin fixed dose combination (FDC) tablet (T, test treatment) compared with co-administration of single tablets of 2.5 mg linagliptin and 500 mg metformin (R, reference treatment) in healthy male and female volunteers.
Methodology:	This was an open-label, randomised, single dose, 2-way crossover trial with 2 treatments (T and R) and 2 treatment sequences (T_R and R_T). The single dose administrations in each treatment period were separated by a washout period of at least 35 days.
No. of subjects:	
planned:	entered: 32 (at least 10 of each gender)
actual:	entered: 32 (15 male and 17 female subjects) Treatment T (linagliptin/metformin FDC tablet): entered and treated: 32 subjects; analysed (for primary endpoint): 32 subjects Treatment R (linagliptin tablet + metformin [Glucophage®] tablet): emtered and treated: 31 subjects; analysed (for primary endpoint): 30 subjects
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers at the age of 18 to 55 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.

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Test product:	Linagliptin/metformin FDC tablet
dose:	2.5 mg linagliptin and 500 mg metformin
mode of admin.:	Oral with 240 mL water after a high-fat, high-caloric meal
batch no.:	B111004867/107133 (Linagliptin/metformin FDC tablet)
Reference products:	Linagliptin tablet + metformin (Glucophage®) tablet
dose:	2.5 mg linagliptin and 500 mg metformin
mode of admin.:	Oral with 240 mL water after a high-fat, high-caloric meal
batch no.:	B111002320 (linagliptin tablet) X1354 (metformin tablet)
Duration of treatment:	Each subject was to receive a single dose of the respective treatment in each of the 2 treatment period (corresponding to a dose of 2.5 mg linagliptin and 500 mg metformin for each treatment). Drug administrations in the 2 treatment periods were separated by a washout period of at least 35 days.
Criteria for evaluation:	
Clinical pharmacology:	The following pharmacokinetic parameters of metformin were analysed as primary endpoints: AUC_{0-tz} and C_{max}. The following pharmacokinetic parameters of metformin were analysed as secondary endpoints: $AUC_{0-\infty}$, t_{max}, and $t_{1/2}$. In addition, the following pharmacokinetic parameters of metformin were assessed as other endpoints: $\%AUC_{tz-\infty}$, AUC_{t1-t2}, λ_z, MRT_{po}, CL/F, and Vz/F.
Safety:	The evaluation of safety was based on monitoring of vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests (haematology, clinical chemistry, and urinalysis), and monitoring of adverse events.

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Statistical methods:

For each of the primary endpoints (AUC_{0-tz} and C_{max} of metformin), the point estimator (gMean) of the intrasubject ratio and its 2-sided 90% confidence interval (CI) were calculated. Bioequivalence criteria were met if these 90% CIs were within 80% and 125%. The statistical model used was an analysis of variance (ANOVA) on ln-transformed parameters including effects for 'sequence', 'subjects nested within sequences', 'period', and 'treatment'. Confidence intervals were based on the residual error from the ANOVA.

Descriptive statistics for all other pharmacokinetic parameters were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

In this trial, 32 subjects received trial medication and 31 subjects completed the trial according to the clinical trial protocol. The trial population consisted of 15 male and 17 female healthy subjects. The mean age was 38.8 years, ranging from 19 to 51 years, and the mean BMI was 23.9 kg/m^2, ranging from 18.7 to 29.1 kg/m^2. All subjects were white with the exception of 1 black subject.

Geometric mean plasma concentration-time profiles of metformin under fed conditions were similar after administration of 2.5 mg linagliptin and 500 mg metformin as either the FDC tablet or as single tablets.

Overall, pharmacokinetic parameters of metformin under fed conditions were similar after administration of 2.5 mg linagliptin and 500 mg metformin as either single tablets or as the FDC tablet. The gMean AUC_{0-tz} was 7210 ng·h/mL for the single tablet treatment and 7060 ng·h/mL for the FDC tablet treatment. The gMean C_{max} was 858 ng/mL for the single tablet treatment and 845 ng/mL for the FDC tablet treatment. The gMean $AUC_{0-\infty}$ was 7330 ng·h/mL for the single tablet treatment and 7170 ng·h/mL for the FDC tablet treatment. Median t_{max} was 4.00 h for both treatments and the terminal half-life $t_{1/2}$ was 9.14 h for the single tablet treatment and 8.03 h for the FDC tablet treatment.

The adjusted gMean ratio of FDC to single tablets for AUC_{0-tz}, C_{max}, and $AUC_{0-\infty}$ are summarised below in Table 1 together with the corresponding 90% CIs and intraindividual gCVs.

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Clinical pharmacology results (continued):

Table 1: Analysis of relative bioavailability of metformin after administration under fed conditions of 2.5 mg linagliptin and 500 mg metformin either as FDC tablet or single tablets

Pharmacokinetic parameter	Adjusted gMean ratio of FDC to single tablets[1] [%]	90% CI of gMean ratio		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Primary endpoints				
AUC_{0-tz} [ng·h/mL]	97.8	93.6	102.1	9.8
C_{max} [ng/mL]	98.8	94.6	103.2	10.0
Secondary endpoint				
$AUC_{0-\infty}$ [ng·h/mL]	97.7	93.6	101.9	9.7

[1] For the calculation of the adjusted gMean, the data of 32 subjects for the FDC tablet treatment and of 30 subjects for single tablet treatment were used.

The 90% CIs for the primary endpoints AUC_{0-tz} and C_{max} as well as for the secondary endpoint $AUC_{0-\infty}$ were within the standard bioequivalence acceptance range of 80 to 125%. The median individual difference of FDC tablet and single tablet treatments for t_{max} was -0.5 h and the 2-sided 90% CI was -0.5 h to 0 h.

Safety results:

Of the 32 entered subjects, 31 subjects received a total dose of 5 mg linagliptin and 1000 mg metformin over the entire course of the trial. The remaining 1 subject only received 2.5 mg linagliptin and 500 mg metformin (FDC tablet, treatment T), before discontinuing the trial due to serious adverse events, which were assessed as not related to the trial medication.

In this trial, a total of 19 subjects (59.4%) reported at least 1 adverse event during the 2 treatment periods. The frequency of subjects with adverse events was comparable after co-administration of the 2 single tablets in treatment R (10 out of 31 subjects, 32.3%) and after administration of the FDC tablet in treatment T (10 out of 32 subjects, 31.3%). During the treatment period, the most frequently reported adverse events overall at the SOC level were nervous system disorders (11 subjects, 34.4%), gastrointestinal disorders (7 subjects, 21.9%), and infections/infestations (3 subjects, 9.4%). On the preferred term level, the most frequently reported adverse events were headache (10 subjects, 31.3%), nausea (4 subjects, 12.5%), and diarrhoea (3 subjects, 9.4%). All other adverse events were reported by 2 subjects (6.3%) or less.

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Safety results (continued):	One subject experienced serious adverse events (motorbike accident and subsequent left clavicle fracture), which occurred during the washout period following the first treatment period and were unrelated to the trial medication. These adverse events required hospitalisation and the subject consequently discontinued the trial. Three subjects experienced severe adverse events. This comprised the subject with 'motorbike accident' and 'left clavicle fracture' described above, one subject 'feeling unwell' due to emotional stress, and one subject with drug-related 'nausea'. All other adverse events were of mild or moderate intensity. The investigator classified adverse events (headache, diarrhoea, nausea, and vomiting) of 3 subjects during single tablet treatment and adverse events (headache, diarrhoea, and nausea) of 4 subjects during FDC tablet treatment as related to the trial medication. This included the 1 case of severe nausea described above. All other adverse events were judged as not drug-related. In this trial, there were no clinically relevant findings with respect to laboratory parameters, vital signs, or ECG recordings. No hypoglycaemic events were reported.
Conclusions:	Bioequivalence for metformin under fed conditions after administration of a 2.5 mg linagliptin/500 mg metformin FDC tablet compared with co-administration of single tablets of 2.5 mg linagliptin and 500 mg metformin was established. Single doses of 2.5 mg linagliptin and 500 mg metformin were safe and well tolerated both as 2 single tablets and as a FDC tablet when given under fed conditions to the healthy male and female subjects in this trial.