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.:** 2009-016642-13	
Name of active ingredient: Linagliptin, metformin		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 02 AUG 2010	**Trial No. / U No.:** 1288.4/U10-2236-02	**Dates of trial:** 12 JAN 2010 – 22 MAR 2010	**Date of revision:** 18 March 2011

Title of trial:	Relative bioavailability of a 2.5 mg lingagliptin+1000 mg metformin fixed dose combination tablet administered with and without food to healthy male and female subjects in an open, randomised, single-dose, two-way crossover Phase I trial
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data from this study have not been published
Clinical phase:	I
Objectives:	To investigate the effect of food on the relative bioavailability of a 2.5 mg linagliptin+1000 mg metformin fixed dose combination (FDC) tablet
Methodology:	Open-label, randomised, single-dose, 2-way crossover design
No. of subjects:	
planned:	entered: 32
actual:	entered: 32 treated: 32 analysed (for primary endpoint): 32
Diagnosis and main criteria for inclusion:	Healthy female and male subjects, age 18 to 55 years, body mass index (BMI) range: 18.5 to 29.9 kg/m^2
Test product:	Linagliptin+metformin FDC tablet (treatment, T)
dose:	2.5 mg linagliptin and 1000 mg metformin
mode of admin.:	Oral with 240 mL of water after a high-fat, high caloric meal
batch no.:	903235
Reference therapy:	Linagliptin+metformin FDC tablet (reference, R)
dose:	2.5 mg linagliptin and 1000 mg metformin
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
batch no.:	903235

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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_{t1-t2}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, and 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 the secondary endpoints AUC_{0-tz} (both analytes) and $AUC_{0-\infty}$ (linagliptin only): point estimators (geometric means [gMeans]) 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'. CIs were based on the residual error from ANOVA. All other parameters: descriptive statistics and tabulated frequencies
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	32 healthy volunteers were entered into the study, 16 (50%) were female. All subjects were white with a mean age of 38.4 years, a mean weight of 75.0 kg, and a mean BMI of 25.4 kg/m^2. Each subject completed the 2 treatment periods and the end-of-study visit.

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Pharmacokinetic results:	A high-fat meal consumed before the administration of the FDC tablet had no influence on the relative bioavailability of linagliptin and metformin with regard to the extent of exposure as determined by AUC_{0-72} (linagliptin) and $AUC_{0-\infty}$ (metformin) compared with the administration of the FDC while fasting (linagliptin AUC_{0-72}: adjusted gMean ratio 98.7%, 90% CI 94.5% to 103.0%; metformin $AUC_{0-\infty}$: adjusted gMean ratio 96.0%, 90% CI 89.2% to 103.2%). After food-intake peak plasma concentrations of linagliptin were slightly lowered (from 4.99 to 4.56 nmol/L), but the 90% CI was still located within the generally applied BE acceptance limits of 80 to 125% (C_{max}: adjusted gMean ratio 91.4%, 90% CI 86.2% to 96.9%). Median t_{max} of linagliptin was also similar under fed (3.00 h) and under fasted conditions (3.50 h). Administration with food reduced the rate of absorption of metformin indicated by a prolongation in median t_{max} (from 2.00 h to 4.00 h) and a decrease in C_{max} by approximately 18% (adjusted gMean ratio 81.9%, 90% CI 76.8% to 87.3%). The secondary PK endpoints $AUC_{0-\infty}$ (linagliptin only) and AUC_{0-tz} (both drugs) were also similar under fasted and fed conditions.
Safety results:	In total 11 subjects (34.4%) reported at least 1 AE during the 2 treatments. The most frequently reported AEs by system organ class (SOC) were infections and infestations (6 subjects, 18.8%), gastrointestinal disorders (4 subjects, 12.5%), nervous system disorders (2 subjects, 6.3%) and general disorders and administration site conditions (2 subjects, 6.3%). Overall, the most frequently reported AEs on the preferred term level were nasopharyngitis (4 subjects, 12.5%), diarrhoea (3 subjects, 9.4%), headache (2 subjects, 6.3%), and fatigue (2 subjects, 6.3%). All AEs were of mild or moderate intensity. Following each treatment, 2 subjects reported at least 1 AE that was study drug-related as assessed by the investigator, most of them were gastrointestinal disorders. All reported AE episodes were recovered until the end of the trial and no subject was discontinued due to an AE. There were no serious AEs. Clinical laboratory tests and the evaluation of vital signs and ECG revealed no safety issues in this study.

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Conclusions:	The relative bioavailability of linagliptin was not relevantly affected when the FDC tablet was administered under fed conditions. Food intake reduced the rate of absorption of metformin but had no influence on the extent of absorption, which is similar to the literature data; therefore it is expected that food has no relevant influence on the efficacy of the linagliptin and metformin FDC tablet. There were no notable differences between the treatment groups with respect to safety and tolerability.