Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** Not applicable	
Name of active ingredient: Linagliptin, metformin		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 30 OCT 2012	**Trial No. / U No.:** 1288.5 / U12-2411-01	**Dates of trial:** 16 FEB 2012 – 04 JUN 2012	**Date of revision:** Not applicable

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Title of trial:	Characterisation of fixed dose combination tablets of linagliptin 2.5 mg/ metformin 850 mg or linagliptin 2.5 mg/metformin 500 mg and relative oral bioavailability compared with single linagliptin 2.5 mg and metformin 850 mg or 500 mg tablets administered together to healthy Chinese male and female volunteers in an open-label, randomised, single-dose, two-way crossover, phase I study
Principal Investigator:	[redacted]
Trial site:	[redacted] China
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objectives:	The objective of this study was to investigate the relative bioavailability of fixed dose combination (FDC) tablets of linagliptin and metformin compared to single tablets of linagliptin and metformin administered together to healthy Chinese volunteers.
Methodology:	Open-label, randomised, single-dose, 2-way crossover study with 2 dose groups
No. of subjects:	
planned:	entered: 48
actual:	entered: 48 Dose group linagliptin 2.5 mg / metformin 850 mg: entered: 24 treated: 24 analysed (for primary endpoints): 24 Dose group linagliptin 2.5 mg / metformin 500 mg: entered: 24 treated: 24 analysed (for primary endpoints): 24
Diagnosis and main criteria for inclusion:	Healthy Chinese volunteers, male and female, age 18 to 40 years, body weight ≥50 kg, body mass index (BMI) 19 to 24 kg/m^2
Test products:	Linagliptin/metformin FDC tablets
dose:	Test treatment 1: linagliptin 2.5 mg / metformin 850 mg Test treatment 2: linagliptin 2.5 mg / metformin 500 mg

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mode of admin.:	Oral with 240 mL water in a standing position after an overnight fast of at least 10 h
batch no.:	FDC linagliptin 2.5 mg / metformin 850 mg: 007249 FDC linagliptin 2.5 mg / metformin 500 mg: 007252
Reference therapies:	Linagliptin tablets and metformin (Glucophage®) tablets
dose:	Reference treatment 1: linagliptin 2.5 mg and metformin 850 mg Reference treatment 2: linagliptin 2.5 mg and metformin 500 mg
mode of admin.:	Oral with 240 mL water in a standing position after an overnight fast of at least 10 h
batch no.:	Linagliptin 2.5 mg: B111002320 Metformin 850 mg: X1486 Metformin 500 mg: X2034
Duration of treatment:	Single dose in each treatment period separated by a washout period of at least 42 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, $AUC_{0-\infty}$ for both analytes Further endpoints: t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, and V_z/F for both analytes
Safety:	Adverse events (AEs), vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, and physical examination
Statistical methods:	The statistical analysis was performed separately for each dose group. The FDC treatments were regarded as the test treatments, the single tablet treatments were regarded as the reference treatments. The point estimates for the ratios of the geometric means ([gMean] test compared to reference treatment) of the primary and secondary pharmacokinetic parameters and their 2-sided 90% confidence intervals (CI) were calculated. The statistical model was an analysis of variance (ANOVA) model on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period' and 'treatment'. For all other parameters descriptive statistics were calculated. Frequencies were tabulated for all categorical parameters.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

A total of 48 healthy subjects, 24 male and 24 female, were entered into the study and treated. All subjects were Asian. The mean age was 28.2 years, ranging from 20 to 38 years, and the mean BMI was 21.95 kg/m^2, ranging from 19.1 to 23.9 kg/m^2. Forty-seven subjects completed both treatment periods, whereas 1 subject was withdrawn after the first treatment period due to the intake of fluconazole and tinidazole to treat a vaginal infection. This subject did not receive the second treatment (FDC tablet of 2.5 mg linagliptin / 850 mg metformin). Two important protocol violations were reported: 1 subject had a positive pregnancy test at the end-of-study visit and 1 subject received prohibited concomitant medications as described above. Both subjects with important protocol violations were included in the primary analysis of relative bioavailability.

Linagliptin 2.5 mg / metformin 850 mg dose group

For linagliptin, the gMean AUC_{0-72} was 248 nmol·h/L (geometric coefficient of variation [gCV] 14.5%) for the FDC and 251 nmol·h/L (gCV 15.3%) for the single tablets and the gMean C_{max} was 6.90 nmol/L (gCV 23.1%) for the FDC and 6.81 nmol/L (gCV 18.2%) for the single tablets. For metformin, the gMean AUC_{0-tz} was 11700 ng·h/mL (gCV 27.9%) for the FDC and 12100 ng·h/mL (gCV 23.2%) for the single tablets and the gMean C_{max} was 1680 ng/mL (gCV 34.8%) for the FDC and 1780 ng/mL (gCV 26.0%) for the single tablets.

Linagliptin 2.5 mg / metformin 500 mg dose group

For linagliptin, the gMean AUC_{0-72} was 266 nmol·h/L (gCV 22.1%) for the FDC and 264 nmol·h/L (gCV 23.8%) for the single tablets and the gMean C_{max} was 7.54 nmol/L (gCV 35.4%) for the FDC and 6.77 nmol/L (gCV 25.9%) for the single tablets. For metformin, the gMean AUC_{0-tz} was 8240 ng·h/mL (gCV 20.8%) for the FDC and 8010 ng·h/mL (gCV 21.3%) for the single tablets and the gMean C_{max} was 1220 ng/mL (gCV 29.1%) for the FDC and 1190 ng/mL (gCV 27.2%) for the single tablets.

For both dose groups and both analytes, gMean plasma concentration-time profiles were similar for the FDC and single tablet treatments.

The adjusted gMean ratios (FDC to single tablets), 90% CIs, and intrasubject gCVs of AUC_{0-72} (linagliptin only), AUC_{0-tz} (metformin only), and C_{max} (both

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Clinical pharmacology results (cont.):

analytes) are summarised in the following table.

	Adjusted gMean ratio (FDC/single tablets) [%]	Two-sided 90% confidence interval		Intraindividual gCV [%]
		Lower limit [%]	Upper limit [%]	
Linagliptin 2.5 mg / 850 mg dose group (FDC N=23, single tablets N=24)				
Linagliptin				
AUC_{0-72}	99.5	94.7	104.5	9.7
C_{max}	101.9	95.4	109.0	13.2
Metformin				
AUC_{0-tz}	97.0	90.6	103.8	13.5
C_{max}	94.6	85.4	104.8	20.5
Linagliptin 2.5 mg / 500 mg dose group (FDC N=24, single tablets N=24)				
Linagliptin				
AUC_{0-72}	100.8	95.1	106.8	11.7
C_{max}	111.4	100.4	123.5	21.2
Metformin				
AUC_{0-tz}	103.0	96.2	110.1	13.6
C_{max}	102.5	92.2	113.9	21.5

For the 2 doses investigated in this study, all 90% CIs for AUC and C_{max} of linagliptin and metformin were contained in the bioequivalence acceptance range of 80 to 125%. Therefore, bioequivalence of the FDC tablet and the single tablets administered together can be assumed.

Safety results:

In the linagliptin 2.5 mg / metformin 850 mg group, 23 subjects received a total dose of 5 mg linagliptin and a total dose of 1700 mg metformin during the trial. The subject who was withdrawn after the first treatment period received a total dose of 2.5 mg linagliptin and a total dose of 850 mg metformin. Each subject in the linagliptin 2.5 mg / metformin 500 mg group received a total dose of 5 mg linagliptin and a total dose of 1000 mg metformin.

A total of 14 subjects (29.2%) experienced at least 1 AE during the 2 treatment periods. Five subjects (10.4%) reported AEs that were assessed by the investigator as drug-related. All AEs reported during the treatment periods were of mild or moderate intensity. All AEs had resolved by the end of the trial. No AEs leading to discontinuation of trial drug, serious AEs, or other significant

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Safety results (cont.):

AEs (according to ICH E3) were reported during the study phase. In the post-study period, 1 subject experienced an AE of severe intensity that was deemed serious: the subject, whose pregnancy test at the end-of-study visit was positive, performed an induced abortion.

In the linagliptin 2.5 mg / metformin 850 mg group, 7 subjects (29.2%) experienced AEs during the treatment period with the single tablets and 3 subjects (13.0%) experienced AEs during the treatment period with the FDC tablet. The most frequently reported AEs in this dose group were rhinorrhoea (2 subjects, 8.3%) and diarrhoea (2 subjects, 8.3%). Four subjects (16.7%) experienced AEs that were assessed by the investigator as drug-related: mild epistaxis, mild nausea, and 2 cases of mild diarrhoea.

In the linagliptin 2.5 mg / metformin 500 mg group, 4 subjects (16.7%) experienced AEs during the treatment period with the single tablets and 1 subject (4.2%) experienced AEs during the treatment period with the FDC tablet. The only AE in this dose group that was reported for more than 1 subject was rhinorrhoea (2 subjects, 8.3%). One subject experienced an AE that was assessed as drug-related (epistaxis).

Clinical laboratory tests, vital signs, and ECG recordings revealed no safety concerns in this study.

Conclusions:

Bioequivalence of FDC tablets containing linagliptin 2.5 mg and metformin 850 or 500 mg to single tablets of 2.5 mg linagliptin and 850 or 500 mg metformin administered together can be assumed when given to healthy male and female Chinese subjects.

For the 2 doses investigated in this trial, both the FDC and single tablet treatments were well tolerated in healthy Chinese subjects and there were no safety concerns.