Clinical Study Synopsis for Public Disclosure

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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.:** 2008-005092-10	
Name of active ingredient: Linagliptin (BI 1356) plus pioglitazone		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 MAY 2010	**Trial No. / U No.:** 1264.1 / U10-1804-01	**Date of trial:** 18 AUG 2009 – 14 DEC 2009	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of two fixed dose combination tablets of linagliptin 5 mg/pioglitazone 45 mg compared with single linagliptin 5 mg and pioglitazone 45 mg tablets administered together to healthy male and female subjects (open, randomised, single dose, three-period crossover phase I trial)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre Biberach, Germany
Publication (reference):	Data from this study have not been published
Clinical phase:	I
Objectives:	To determine the relative bioavailability of 2 different formulations of a 5 mg linagliptin (BI 1356)/45 mg pioglitazone fixed dose combination (FDC) tablet, formulation C5 and formulation C8, compared with the mono-components linagliptin and pioglitazone administered together (R, reference therapy)
Methodology:	Open-label, randomised, 3-period crossover trial
No. of subjects:	
planned:	Entered: 40
actual:	Entered: 40 Treated: 39 Analysed for primary endpoint: 39
Diagnosis and main criteria for inclusion:	Healthy male and female subjects, between 18 and 55 years of age; body mass index between 18.5 and 29.9 kg/m^2

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Test product:	Linagliptin/pioglitazone, FDC formulation C5, Treatment 1 (T1); film-coated tablet
dose:	5 mg/45 mg
mode of admin.:	Oral with 240 mL of water
batch no.:	B091002621
Test product:	Linagliptin/pioglitazone, FDC formulation C8, Treatment 2 (T2); film-coated tablet
dose:	5 mg/45 mg
mode of admin.:	Oral with 240 mL of water
batch no.:	B091002706
Reference therapy:	Linagliptin tablet and pioglitazone tablet (Actos®), Reference (R)
dose:	5 mg and 45 mg
mode of admin.:	Oral with 240 mL of water
batch no.:	956146 (linagliptin), C14282 (pioglitazone)
Duration of treatment:	Three single doses separated by a washout period of at least 35 days
Criteria for evaluation: **Clinical pharmacology:**	Relative bioavailability was primarily determined on the basis of the parameters: $AUC_{0-\infty}$ (pioglitazone), AUC_{0-72} (linagliptin) and C_{max} (both analytes). Additionally, the following secondary endpoints were evaluated: AUC_{0-72} (pioglitazone only), $AUC_{0-\infty}$ (linagliptin only), and AUC_{0-tz} (both analytes) Additional pharmacokinetic parameters were calculated as appropriate
Safety:	Physical examination, vital signs (blood pressure, pulse rate),12-lead electrocardiogram, clinical laboratory parameters (haematology, clinical chemistry and urinalysis), adverse events (AEs), overall tolerability

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Statistical methods: Point estimators (geometric means) of the median intra-subject ratios of the primary and some of the secondary endpoints and their 2-sided 90% confidence intervals were calculated. The statistical model was an 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. Descriptive statistics for all other parameters were calculated. Frequencies were tabulated for all categorical parameters.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Concomitant administration of single doses of 5 mg linagliptin and 45 mg pioglitazone either as the FDC-C5 (T1) tablet, the FDC-C8 (T2) tablet, or as mono-components (2 single tablets), resulted in a comparable extent and rate of linagliptin exposure, as determined by AUC_{0-72} (FDC-C5: 264 nmol·h/L, FDC-C8: 251 nmol·h/L, single tablet administration: 262 nmol·h/L) and C_{max} (FDC-5: 7.85 nmol/L, FDC-8: 7.62 nmol/L, single tablet administration: 8.20 nmol/L).

The extent of pioglitazone exposure, as determined by AUC_{0-tz}, was about 12% lower after the administration of the FDC-C5 tablet (11600 ng·h/mL), and about 26% lower after the administration of the FDC-C8 tablet (9500 ng·h/mL), when compared with the 2 single tablet administration (13200 ng·h/mL). Similarly, the extent of pioglitazone exposure, as determined by $AUC_{0-\infty}$, was about 13.5% lower after the administration of the FDC-C5 tablet (11900 ng·h/mL) and about 26% lower after the administration of the FDC-C8 tablet (9940 ng·h/mL), when compared with the 2 single tablet administration (13900 ng·h/mL).

The rate of pioglitazone exposure, as determined by C_{max}, was about 15% higher after administration of the FDC-C5 tablet (1230 ng/mL), and about 8% lower after administration of the FDC-C8 tablet (961 ng/mL), when compared with the single tablet administration (1060 ng/mL). The C_{max} was reached 0.5 h earlier with the FDC-C5 tablet administration (median t_{max} 1.50 h), and 1 h earlier with the FDC-C8 tablet administration (median t_{max} 1.00 h), when compared with the single tablet administration (median t_{max} 2.00 h).

The adjusted gMean Test/Reference ratios, the associated 90% CIs, and the intra-individual geometric coefficients of variation (gCV) are summarised in the following table (as determined by ANOVA analysis).

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Clinical pharmacology results (cont.):

Parameter	N_T/N_R	Intra-indiv. gCV [%]	Adjusted gMean ratio (FDC/ Lina+Pio)	Two-sided 90% confidence interval	
				Lower limit [%]	Upper limit [%]
PK endpoint of **linagliptin**					
FDC-C5 vs. mono-components					
AUC_{0-72} [nmol·h/L]	38/39	15.9	101.5	95.5	107.8
C_{max} [nmol/L]	38/39	25.6	96.5	87.7	106.3
FDC-C8 vs. mono-components					
AUC_{0-72} [nmol·h/L]	36/39	15.9	96.3	90.6	102.4
C_{max} [nmol/L]	36/39	25.6	93.1	84.4	102.6
PK endpoint of **pioglitazone**					
FDC-C5 vs. mono-components					
$AUC_{0-\infty}$ [ng·h/mL]	38/39	25.2	86.5	78.7	95.1
AUC_{0-tz} [ng·h/mL]	38/39	25.5	88.4	80.3	97.3
C_{max} [ng/mL]	38/39	39.3	114.6	99.1	132.4
FDC-C8 vs. mono-components					
$AUC_{0-\infty}$ [ng·h/mL]	36/39	25.2	73.8	67.0	81.2
AUC_{0-tz} [ng·h/mL][1]	36/39	25.5	73.8	66.9	81.4
C_{max} [ng/mL]	36/39	39.3	91.6	79.0	106.1

[1] AUC_{0-tz} was pre-specified as a secondary endpoint parameter only

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Safety results:

Overall, 29 subjects (74.4%) reported at least 1 AE during the on-treatment periods and of those, 14 subjects required therapy for at least 1 AE; all subjects who reported AEs recovered. None of the reported AEs were assessed as drug-related by the investigator. No deaths, or other serious AEs, significant or other significant AEs were reported in this study. One subject discontinued from the trial after being reported with a severe AE (dental inflammation) during the washout after the first administration of trial medication. Two subjects did not receive the second scheduled treatment due to AEs (nasopharyngitis) reported in the washout after the first administration of trial drug, but continued with the trial in the third treatment period.

Minor numerical differences in the incidences of AEs were observed between the 3 treatments (subjects with at least 1 AE on-treatment: 2 single tablet administration: 46.2% of treated subjects; FDC-C5: 39.5%; FDC-C8: 38.9%); these differences were not considered clinically relevant. The most frequently reported AEs were headache (18 subjects, 46.2%), nasopharyngitis (9 subjects, 23.1%), and oropharyngeal pain (5 subjects, 12.8%). The majority of AEs were of mild or moderate intensity. Three subjects reported AEs of severe intensity, and all severe AEs were reported at least 7 days following treatment administration. These severe AEs were reported by subject no. 33 (dental inflammation), by subject no.18 (headache, dysmenorrhoea, and nasopharyngitis), and by subject no. 23 (back pain).

Based on the safety and tolerability results, all 3 single dose treatments of 5 mg linagliptin and 45 mg pioglitazone were well tolerated in healthy male and female subjects.

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Conclusions:

Concomitant administration of 5 mg linagliptin and 45 mg pioglitazone either as fixed dose combinations FDC-C5 (T1) or FDC-C8 (T2), or as mono-components (2 single tablets), resulted in a comparable extent and rate of linagliptin exposure. The standard bioequivalence (BE) acceptance criteria were met for all endpoints. After administration of FDC-C5, the extent of pioglitazone exposure was about 12% lower for AUC_{0-tz}, about 13.5% lower for $AUC_{0-\infty}$, the maximum plasma concentrations were about 15% higher, and median t_{max} was 0.5 h earlier when compared with the 2 single tablets. This indicated a slightly increased absorption rate, and the standard BE acceptance criteria were met only for AUC_{0-tz}. After administration of FDC-C8, the extent of pioglitazone exposure was reduced by about 26% for both AUC_{0-tz} and $AUC_{0-\infty}$, the maximum plasma concentrations were about 8% lower, and the median t_{max} was 1 h earlier when compared with the 2 single tablets. The standard BE acceptance criteria were not met for any endpoint. Based on the safety and tolerability results, all 3 single dose treatments of 5 mg linagliptin and 45 mg pioglitazone were well tolerated in healthy male and female subjects.