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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022649-29	
Names of active ingredients: Linagliptin / pioglitazone		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 NOV 2011	**Trial No. / U No.:** 1264.14 / U11-2592-01	**Dates of trial:** 11 JAN 2011 – 30 MAY 2011	**Date of revision:** Not applicable

Title of trial:	Bioequivalence of a fixed dose combination tablet of linagliptin 5 mg / pioglitazone 30 mg compared with its mono-components in healthy male and female subjects (an open-label, randomised, single-dose, replicate design study with two treatments in four crossover periods)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre Biberach, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objective:	The objective was to demonstrate bioequivalence of a linagliptin 5 mg / pioglitazone 30 mg fixed dose combination (FDC) tablet (Test, T) compared with the individual tablets administered together (Reference, R).
Methodology:	Open-label, randomised, single-dose, replicate design crossover study with 2 treatments and 4 treatment periods
No. of subjects:	
planned:	entered: 64
actual:	entered: 64 (32 in sequence TRTR and 32 in sequence RTRT) Test treatment: FDC tablet treated: 62 analysed (for primary endpoints): 62 Reference treatment: linagliptin and pioglitazone individual tablets treated: 63 analysed (for primary endpoints): 63
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥18 and ≤55 years, body mass index (BMI) ≥18.5 and ≤29.9 kg/m^2
Test product:	Linagliptin / pioglitazone FDC tablet
dose:	Linagliptin 5 mg and pioglitazone 30 mg
mode of admin.:	Oral administration with 240 mL water after an overnight fast
batch no.:	005213

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Reference therapy:	Linagliptin tablet and pioglitazone tablet (Actos®)
dose:	Linagliptin 5 mg and pioglitazone 30 mg
mode of admin.:	Oral administration with 240 mL water after an overnight fast
batch no.:	Linagliptin: 4000427, Actos®: B101003041 (A16356 Takeda Pharma)
Duration of treatment:	One day (single dose) in each treatment period. Drug administrations were separated by washout periods of at least 35 days.
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints: AUC_{0-72} (linagliptin), AUC_{0-tz} (pioglitazone), and C_{max} (both analytes) Secondary endpoints: AUC_{0-tz} (linagliptin), $AUC_{0-\infty}$ and t_{max} (both analytes) Additionally, pharmacokinetic parameters of the active metabolites M-III and M-IV of pioglitazone were determined.
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, analysis of adverse events (AE), and tolerability assessment
Statistical methods:	The statistical model was an analysis of variance (ANOVA) model on the logarithmic scale, adapted for the replicate design. It included effects for 'sequence', 'subject', 'period', and 'treatment'. The effect 'subject' was considered as random, whereas the other effects were considered as fixed. The (unscaled) average bioequivalence method was the primary analysis for AUC_{0-72} and C_{max} of linagliptin. For both parameters, the point estimator and associated 2-sided 90% confidence interval (CI) for the geometric mean (gMean) within-subject ratio of Test to Reference were calculated. Bioequivalence was demonstrated if the 90% CIs were contained in the 80 to 125% acceptance range for bioequivalence. A similar analysis was performed for the secondary endpoints AUC_{0-tz} and $AUC_{0-\infty}$ of linagliptin and also for pioglitazone endpoints. The scaled average bioequivalence (SABE) method was the primary analysis for AUC_{0-tz} and C_{max} of pioglitazone. A similar analysis was performed for the secondary endpoint $AUC_{0-\infty}$ of pioglitazone. Scaling of the bioequivalence

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Statistical methods (cont.):

acceptance range was applicable if the within-subject variability of the reference treatment was ≥30% for an endpoint.

For all other parameters, descriptive statistics were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

The study population consisted of 64 healthy subjects, 26 female and 38 male. All subjects were white. The mean age was 37.9 years, ranging from 20 to 55 years, and the mean BMI was 24.24 kg/m^2, ranging from 19.2 to 28.7 kg/m^2. Fifty-nine subjects completed the planned observation time, whereas 4 subjects discontinued the study prematurely due to AEs and 1 subject withdrew her consent due to personal reasons and missed the last treatment period. In addition, 1 subject missed the second treatment period due to an AE but underwent the following treatment periods. Overall, 62 subjects provided data for the test treatment and 63 subjects provided data for the reference treatment.

Concomitant administration of single doses of 5 mg linagliptin and 30 mg pioglitazone either as FDC tablet or as individual tablets resulted in a comparable rate and extent of linagliptin exposure (as determined by AUC_{0-72} and C_{max}). Geometric mean C_{max} and AUC_{0-72} of linagliptin were 8.65 nmol/L (between-subject geometric coefficient of variation [gCV] 33.3%) and 278 nmol·h/L (gCV 20.6%) after administration of the FDC tablet, compared with 9.09 nmol/L (gCV 31.2%) and 279 nmol·h/L (gCV 20.6%) after administration of the individual tablets. Maximum linagliptin plasma concentrations were observed after a median t_{max} of 1.73 h (range 0.677 h to 6.93 h) for the FDC tablet and 1.50 h (range: 0.577 h to 6.93 h) for the individual tablets.

Geometric mean C_{max} of pioglitazone was 806 ng/mL (gCV 58.5%) after administration of the FDC tablet and thus approximately 4% lower than after administration of the individual tablets (843 ng/ml, gCV 42.7%); gMean AUC_{0-tz} of pioglitazone was 6370 ng·h/mL (gCV 49.3%) after administration of the FDC tablet and thus approximately 20% lower than after administration of the individual tablets (8100 ng·h/mL, gCV 41.2%). Maximum plasma concentrations of pioglitazone were reached 30 min earlier with the FDC tablet than with the individual tablets: median t_{max} was 1.00 h (range 0.667 h to 5.66 h) for the FDC tablet and 1.50 h (range: 0.650 h to 4.90 h) for the individual tablets. Also, a plateau around peak plasma concentration was observed for the

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Clinical pharmacology results (cont.):

individual tablets but not for the FDC tablet.

For linagliptin, the adjusted gMean ratio Test/Reference was 94.17% (90% CI 89.08% to 99.55%) for C_{max} and 99.92% (90% CI 97.11% to 102.81%) for AUC_{0-72}. Thus, standard acceptance criteria for bioequivalence (90% CI within 80 to 125%) were met for linagliptin endpoints.

For C_{max} of pioglitazone, the adjusted gMean ratio Test/Reference was 97.31% (90% CI 88.90% to 106.51%). Thus, standard bioequivalence acceptance criteria were met for C_{max}. Bioequivalence could also be shown based on the SABE criterion (SABE was applicable as the within-subject variability of the reference treatment was 31% for C_{max} of pioglitazone). For AUC_{0-tz} and $AUC_{0-\infty}$, the adjusted gMean ratios Test/Reference were 79.99% (90% CI 74.65% to 85.72%) and 80.79% (90% CI 75.60% to 86.34%), respectively. Hence, the standard bioequivalence acceptance criteria were not met for both AUC_{0-tz} and $AUC_{0-\infty}$. As the within-subject variability for the reference treatment was low for these parameters (18.97% for AUC_{0-tz} and 18.41% for $AUC_{0-\infty}$), the SABE criterion could not be applied for the pioglitazone AUCs.

Safety results:

Of the 64 entered subjects, 58 were administered 4 single doses of the trial medication (i.e. a total dose of 20 mg linagliptin and 120 mg pioglitazone) as planned. Two subjects received 3 single doses, 1 subject received 2 single doses, and 3 subjects received 1 single dose of the trial medication.

A total of 31 subjects (48.4%) reported at least 1 AE during the study:
20 subjects (32.3%) after treatment with the FDC tablet and 18 subjects (28.6%) after treatment with the individual tablets. The most frequently reported AEs overall were headache (11 subjects, 17.2%) and nasopharyngitis (8 subjects, 12.5%). One subject experienced a serious AE (moderate gastrointestinal pain that led to hospitalisation) and discontinued the study after the first treatment period. The event was not considered to be related to the trial medication. In addition, 3 other subjects discontinued the trial due to AEs, which were therefore classified as 'other significant'. Only 1 of the AEs leading to discontinuation was considered drug-related (diarrhoea).

Two subjects (3.1%) had influenza that was rated as severe; 1 subject after treatment with the FDC tablet, the other one after treatment with the individual tablets. All other AEs were of mild or moderate intensity. Two subjects (3.1%) reported AEs that were assessed as drug-related: 1 subject reported headache,

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Safety results (cont.): nausea, and vomiting after treatment with the FDC tablet, and 1 subject reported diarrhoea after treatment with the individual tablets.

There were no relevant findings with respect to clinical laboratory parameters, vital signs, or ECG recordings. The assessment of tolerability was 'good' for all subjects and all treatment periods except for the 2 subjects with drug-related AEs whose tolerability assessment was 'satisfactory' in the first treatment period.

Conclusions: Concomitant administration of 5 mg linagliptin and 30 mg pioglitazone either as FDC tablet or individual tablets resulted in a comparable rate and extent of linagliptin exposure. The standard bioequivalence acceptance criteria were met for all endpoints. After administration of the FDC, the maximum exposure for pioglitazone was comparable with the individual tablets; median time to reach maximal concentrations was slightly earlier for the FDC. The total exposure for pioglitazone was approximately 20% lower after administration of the FDC. Standard bioequivalence acceptance criteria as well as scaled average bioequivalence (SABE) acceptance criteria were met for C_{max}. For AUC_{0-tz}, standard bioequivalence acceptance criteria were not met, while SABE criteria were not applicable.

Based on the safety and tolerability results, both single dose treatments of 5 mg linagliptin and 30 mg pioglitazone were well tolerated in healthy male and female subjects.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and/or results for primary and 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**
PK parameters of linagliptin after administration as a single tablet	Table 15.6.2.1: 25
PK parameters of linagliptin after administration as a fixed dose combination (FDC)	Table 15.6.2.1: 26
PK parameters of pioglitazone after administration as a single tablet	Table 15.6.2.1: 29
PK parameters of pioglitazone after administration as a fixed dose combination (FDC)	Table 15.6.2.1: 30

Table 15.6.2.1: 25 Noncompartmental pharmacokinetic parameters (gMean of two periods per subject) of linagliptin after single oral administration of 5 mg linagliptin and 30 mg pioglitazone as single tablets (R) with descriptive statistics

Single tablets	Noncompartmental parameters of linagliptin							
Subject	AUC_{0-24} [nmol*h/L]	AUC_{0-72} [nmol*h/L]	AUC_{0-tz} [nmol*h/L]	t_z [h]	$AUC_{0-\infty,1}$ [nmol*h/L]	$\%AUC_{tz-\infty,1}$ [%]	$AUC_{0-\infty,2}$ [nmol*h/L]	$\%AUC_{tz-\infty,2}$ [%]
N	63	63	63	63	63	63	63	63
gMean	129	279	279	72.0	447	36.9	448	37.1
gCV [%]	20.3	20.6	20.6	0.0138	24.5	14.3	24.4	14.1
Mean	132	284	284	72.0	460	37.3	461	37.4
CV [%]	20.4	20.7	20.7	0.0138	25.0	14.1	25.0	13.9
SD	26.9	58.9	58.9	0.00992	115	5.24	115	5.19
Min	76.4	168	168	72.0	272	26.0	272	26.3
Median	128	270	270	72.0	439	37.2	439	37.0
Max	219	474	474	72.1	896	48.0	905	47.8

AUC0-oo,1 =predicted; AUC0-oo,2 = observed; %AUCtz-oo,1 = predicted; %AUCtz-oo,2 = observed

Source data: Section 15.6, Table 1.1: 3

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Table 15.6.2.1: 26 Noncompartmental pharmacokinetic parameters (gMean of two periods per subject) of linagliptin after single oral administration of 5 mg linagliptin and 30 mg pioglitazone as FDC tablet (T) with descriptive statistics

FDC tablet	Noncompartmental parameters of linagliptin							
Subject	AUC_{0-24} [nmol*h/L]	AUC_{0-72} [nmol*h/L]	AUC_{0-tz} [nmol*h/L]	t_z [h]	$AUC_{0-\infty,1}$ [nmol*h/L]	$\%AUC_{tz-\infty,1}$ [%]	$AUC_{0-\infty,2}$ [nmol*h/L]	$\%AUC_{tz-\infty,2}$ [%]
N	62	62	62	62	62	62	62	62
gMean	128	278	278	72.0	455	36.9	456	37.0
gCV [%]	20.4	20.6	20.6	0.00768	27.4	25.5	27.5	27.0
Mean	130	284	284	72.0	471	37.9	472	38.0
CV [%]	20.1	20.2	20.2	0.00768	26.5	20.2	26.5	20.4
SD	26.2	57.3	57.3	0.00553	125	7.65	125	7.74
Min	86.3	172	172	72.0	215	9.67	213	8.14
Median	129	280	280	72.0	443	38.0	443	38.0
Max	191	443	443	72.0	792	52.0	789	52.8

AUC0-oo,1 =predicted; AUC0-oo,2 = observed; %AUCtz-oo,1 = predicted; %AUCtz-oo,2 = observed

Source data: Section 15.6, Table 1.1: 4

Table 15.6.2.1: 29 Noncompartmental pharmacokinetic parameters (gMean of two periods per subject) of pioglitazone after single oral administration of 5 mg linagliptin and 30 mg pioglitazone as single tablets (R) with descriptive statistics

Single tablets	Noncompartmental parameters of pioglitazone								
Subject	AUC_{0-24} [ng*h/mL]	AUC_{0-72} [ng*h/mL]	AUC_{0-tz} [ng*h/mL]	t_z [h]	$AUC_{0-\infty,1}$ [ng*h/mL]	$\%AUC_{tz-\infty,1}$ [%]	$AUC_{0-\infty,2}$ [ng*h/mL]	$\%AUC_{tz-\infty,2}$ [%]	C_{max} [ng/mL]
N	63	63	63	63	63	63	63	63	63
gMean	6960	8140	8100	62.7	8300	0.932	8290	0.916	843
gCV [%]	40.9	40.5	41.2	23.3	40.4	150	40.4	144	42.7
Mean	7500	8760	8740	64.2	8920	1.71	8920	1.66	909
CV [%]	39.3	39.4	39.7	18.8	39.0	143	39.0	145	37.1
SD	2940	3450	3470	12.1	3480	2.45	3480	2.42	337
Min	2820	3010	2940	24.0	3010	0.0944	3010	0.0962	297
Median	6970	7820	7820	72.0	7940	0.978	7930	0.948	861
Max	17100	20600	20600	72.1	20700	14.6	20700	13.7	1790

AUC0-oo,1 =predicted; AUC0-oo,2 = observed; %AUCtz-oo,1 = predicted; %AUCtz-oo,2 = observed

Source data: Section 15.6, Table 1.1: 9

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Table 15.6.2.1: 30 Noncompartmental pharmacokinetic parameters (gMean of two periods per subject) of pioglitazone after single oral administration of 5 mg linagliptin and 30 mg pioglitazone as FDC tablet (T) with descriptive statistics

FDC tablet	Noncompartmental parameters of pioglitazone								
Subject	AUC_{0-24} [ng*h/mL]	AUC_{0-72} [ng*h/mL]	AUC_{0-tz} [ng*h/mL]	t_z [h]	$AUC_{0-\infty,1}$ [ng*h/mL]	$\%AUC_{tz-\infty,1}$ [%]	$AUC_{0-\infty,2}$ [ng*h/mL]	$\%AUC_{tz-\infty,2}$ [%]	C_{max} [ng/mL]
N	62	62	62	62	62	62	62	62	62
gMean	5600	6390	6370	61.2	6580	1.13	6590	1.13	806
gCV [%]	50.9	48.7	49.3	23.6	47.5	138	47.5	137	58.5
Mean	6200	7030	7020	62.7	7210	2.49	7220	2.49	906
CV [%]	42.7	42.5	42.7	20.0	41.5	243	41.5	244	42.0
SD	2650	2990	3000	12.5	2990	6.04	2990	6.09	380
Min	1420	1560	1510	33.9	1560	0.219	1560	0.236	136
Median	6080	6720	6690	72.0	6780	0.915	6780	0.923	946
Max	14000	16700	16700	72.0	16900	43.2	16900	43.6	1720

AUC0-oo,1 =predicted; AUC0-oo,2 = observed; %AUCtz-oo,1 = predicted; %AUCtz-oo,2 = observed

Source data: Section 15.6, Table 1.1: 10

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