Boehringer Ingelheim

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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jentadueto®			
BI Investigational Product: Linagliptin (BI 1356) / metformin		**Page:** 1 of 4	
Report Date: 05 Aug 2014	**Trial No. / Doc. No.:** 1288.21 / c02325770-01	**Dates of Trial:** 28 Nov 2013 – 30 Jan 2014	**Date of Revision:** Not applicable

Title of Trial:	An open-label, randomised, single-dose, two-way crossover study in healthy male and female subjects to evaluate the bioequivalence of Jentadueto® (two fixed dose combination tablets of linagliptin 2.5 mg and metformin 500 mg) compared with the free combination of linagliptin 5 mg and metformin 1000 mg tablets under fasting conditions
Principal Investigator:	[redacted]
Trial Site:	[redacted]
Publications:	Data from this trial have not been published at the time of this report.
Clinical Phase:	I
Objective:	The objective was to demonstrate bioequivalence of two 2.5 mg linagliptin / 500 mg metformin fixed dose combination (FDC) tablets compared with the free combination of linagliptin 5 mg and metformin 1000 mg tablets.
Methodology:	This was a randomised, open-label, single-dose, 2-way crossover trial.
No. of Subjects:	
Planned:	To be entered: 36
Actual:	Entered: 36 Linagliptin/metformin FDC: Treated: 36 Analysed (for primary endpoints): 36 Free combination of linagliptin and metformin tablets: Treated: 36 Analysed (for primary endpoints): 34
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male and female subjects, age 18 to 45 years, body mass index (BMI) 18.50 to 24.99 kg/m^2
BI Investigational Product:	Linagliptin/metformin FDC tablet (Jentadueto®)
Dose:	5 mg linagliptin / 1000 mg metformin (given as two 2.5 mg linagliptin / 500 mg metformin FDC tablets)
Mode of Admin.:	Oral with 240 mL water after an overnight fast of at least 10 h
Batch No.:	106913

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jentadueto®			
BI Investigational Product: Linagliptin (BI 1356) / metformin		**Page:** 2 of 4	
Report Date: 05 Aug 2014	**Trial No. / Doc. No.:** 1288.21 / c02325770-01	**Dates of Trial:** 28 Nov 2013 – 30 Jan 2014	**Date of Revision:** Not applicable

Comparator Products:	Linagliptin tablet (Trajenta®) and metformin tablet (Glucophage®)
Dose:	5 mg linagliptin, 1000 mg metformin
Mode of Admin.:	Oral with 240 mL water after an overnight fast of at least 10 h
Batch No.:	4000876 (Trajenta®), 802859 (Glucophage®, Merck Santé)
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-tz} and C_{max} for metformin Secondary endpoints: $AUC_{0-\infty}$ for linagliptin and metformin, AUC_{0-tz} for linagliptin
Safety:	The evaluation of safety was based on: monitoring of adverse events (AEs), clinical laboratory tests, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), and physical examination. Endpoints of safety were considered to be further endpoints in this study.
Statistical Methods:	The assessment of bioequivalence was based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the primary endpoints using an acceptance range of 80 to 125% for AUC and 75 to 133% for C_{max}. This method is equivalent to the two 1-sided t-tests procedure, each at the 5% significance level. The statistical model was an analysis of variance (ANOVA) on the log-transformed (natural logarithm) parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. For co-primary analyses, 2 models were fitted: a model considering all effects as fixed as well as the same model which included 'subjects within sequences' as a random effect. CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated. No interim analysis was performed.
SUMMARY - CONCLUSIONS:	
Trial Subjects and Compliance with Trial Protocol:	A total of 36 healthy subjects were entered into the trial and treated. All subjects completed the trial according to protocol. Of the 36 entered subjects, 16 subjects (44.4%) were male and 20 subjects (55.6%) were female. All subjects were White. The age (mean and standard deviation [SD]) of the treated subjects was 25.0 (6.2) years, and the BMI (mean and SD) was 21.93 (1.92) kg/m^2. No important protocol violations were reported.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jentadueto®			
BI Investigational Product: Linagliptin (BI 1356) / metformin		**Page:** 3 of 4	
Report Date: 05 Aug 2014	**Trial No. / Doc. No.:** 1288.21 / c02325770-01	**Dates of Trial:** 28 Nov 2013 – 30 Jan 2014	**Date of Revision:** Not applicable

Clinical Pharmacology Results:

Geometric mean (gMean) plasma concentration-time profiles and pharmacokinetic parameters of linagliptin and metformin were similar for the FDC and the free combination of linagliptin and metformin tablets. The adjusted gMean values, the adjusted gMean ratios FDC to free combination, 2-sided 90% CIs, and intraindividual geometric coefficient of variation (gCV) values for the primary and secondary endpoints are summarised in the following table.

Table 1: Bioequivalence analysis of linagliptin and metformin after administration of 5 mg linagliptin and 1000 mg metformin as 2 FDC tablets (2.5 mg/500 mg) or free combination (analysis including 'subjects within sequences' as a fixed effect)

	Adjusted gMean FDC (N=34)[1]	Adjusted gMean free combination (N=34)[1]	Adjusted gMean ratio FDC/free combination [%]	Two-sided 90% CI (upper limit, lower limit) [%]	Intra-individual gCV [%]
Linagliptin					
Primary endpoints					
AUC_{0-72} [nmol·h/L]	293	285	102.9	(98.4, 107.7)	11.0
C_{max} [nmol/L]	10.3	9.44	109.1	(98.3, 121.0)	25.6
Secondary endpoints					
$AUC_{0-\infty}$ [nmol·h/L]	467	474	98.5	(92.2, 105.2)	16.2
AUC_{0-tz} [nmol·h/L]	293	285	102.9	(98.4, 107.7)	11.0
Metformin					
Primary endpoints					
AUC_{0-tz} [ng·h/mL]	13 000	12 364	105.1	(99.6, 110.9)	13.1
C_{max} [ng/mL]	1837	1736	105.8	(98.5, 113.7)	17.6
Secondary endpoint					
$AUC_{0-\infty}$ [ng·h/mL]	13 380	12 789	104.6	(99.3, 110.3)	12.8

[1] Two of the 36 subjects were excluded from the analysis with 'subjects within sequences' as a fixed effect for both periods because they had no quantifiable linagliptin plasma concentrations in the period with the free combination.

The analysis with 'subjects within sequences' as a random effect (FDC: N=36; free combination: N=34) yielded similar results. As all adjusted gMean ratios and 90% CIs for the primary and secondary endpoints were within the pre-defined acceptance limits of 80 to 125% for AUC and 75 to 133% for C_{max}, bioequivalence between the FDC tablets and the free combination was established.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jentadueto®			
BI Investigational Product: Linagliptin (BI 1356) / metformin		**Page:** 4 of 4	
Report Date: 05 Aug 2014	**Trial No. / Doc. No.:** 1288.21 / c02325770-01	**Dates of Trial:** 28 Nov 2013 – 30 Jan 2014	**Date of Revision:** Not applicable

Safety Results:

No serious AEs, no severe AEs, no other significant AEs (according to ICH E3), and no protocol-specified AEs of special interest were reported. No subject discontinued trial participation due to an AE.

Five subjects (13.9%) reported headache of mild intensity during the trial: 4 subjects (11.1%) in the treatment period with the free combination and 1 subject (2.8%) in the treatment period with the FDC tablets. All cases of headache were assessed by the investigator as drug-related. No other AEs were reported in this trial.

There were no clinically relevant findings with respect to clinical laboratory parameters, vital signs, ECG, or physical examination.

Conclusions:

The bioequivalence of linagliptin and metformin was investigated after administration of 2 linagliptin 2.5 mg / metformin 500 mg FDC tablets (Jentadueto®) compared with the free combination of linagliptin 5 mg and metformin 1000 mg under fasted conditions. FDC to free combination gMean ratios and 2-sided 90% CIs for AUC_{0-72} and C_{max} of linagliptin and AUC_{0-tz} and C_{max} of metformin were within the pre-defined acceptance ranges (80 to 125% for AUC and 75 to 133% for C_{max}). Thus, bioequivalence between the FDC and the free combination was established.

The FDC tablets and the free combination of linagliptin and metformin tablets were well tolerated when administered to healthy male and female subjects.