CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208026Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208026
Link to EDR	\\CDSESUB1\evsprod\NDA208026\0000
Submission Date(s)	July 27, 2015
Submission Type	505(b)(1)
Brand Name	JENTADUETO® XR
Generic Name	Linagliptin and metformin HCl extended-release fixed dose combination tablets
Dosage Form and Strength	Tablets; 2.5 mg linagliptin/1000 mg metformin; 5 mg linagliptin/1000 mg metformin
Route of Administration	Oral
Proposed Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate
Applicant	Boehringer Ingelheim
Associated INDs	(b) (4)
OCP Review Team	Sang M. Chung, Ph.D., Manoj Khurana, Ph.D.

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1 Executive Summary

The applicant has submitted NDA 208026 for JENTADUETO® XR, the fixed dose combination (FDC XR) of linagliptin and metformin extended-release, as a 505(b)(1) based on the bioequivalence (BE) of FDC XR to co-administration of linagliptin and metformin hydrochloride (HCl) extended-release in healthy volunteers. The proposed indication is an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

The applicant is the sponsor of linagliptin (TRADJENTA®, NDA 201280) and JENTADUETO® (FDC of linagliptin and metformin HCl twice daily, NDA 201281), and provides a Letter of Authorization from the sponsor of metformin extended-release product (GLUMETZA®, NDA 021748).

The applicant refers pertinent labeling information of GLUMETA® and JENTADUETO® for JENTADUETO® XR. The following proposed starting dose is acceptable referring those of GLUMETA® and JENTADUETO®:

- In patients currently not treated with metformin, initiate treatment with 5 mg linagliptin/1000 mg metformin hydrochloride extended-release once daily (refer 2.5 mg linagliptin/500 mg metformin twice daily as initial treatment for JENTADUETO®)
- In patients already treated with metformin, the recommended total daily starting dose of JENTADUETO® XR is 5 mg linagliptin and a similar total daily dose of metformin
- In patients already treated with TRADJENTA® and metformin or JENTADUETO® switch to JENTADUETO® XR containing 5 mg of linagliptin total daily dose and a similar total daily dose of metformin

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed NDA 208026 for JENTADUETO® XR and recommends approval.

1.2 Post-Market Requirements and Commitments

None

2 Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

The efficacy and safety of linagliptin given once daily as add-on to metformin given twice daily was adequately demonstrated using Phase 3 study results in the original NDA for TRADJENTA® (linagliptin). In addition, the efficacy and safety of FDC (linagliptin/metformin)

was shown with Phase 3 study results of the original NDA for JENTADUETO® including those of initial combination therapy with linagliptin and metformin based on results of factorial design study, which included efficacy/safety evaluation of the 2.5 mg linagliptin/500 mg metformin IR twice daily treatment and unique to JENTADUETO® development program (refer details to the Clinical Pharmacology Review for JENTADUETO® by Dr. Khurana dated 10/11/2011).

The applicant used BE study results as the pivotal supporting information for JENTADUETO® XR referencing co-administration of TRADJENTA® and GLUMETZA®. The BE approach has been part of other FDC XR development in the same class (DPP-4 inhibitors and metformin extended-release formulations such as KOMBIGLYZE® XR and JANUMET® XR). Basis of the BE approach for FDC XR development is that the efficacy and safety of co-administration following twice daily dosing is available, and reference product of metformin XR has adequate clinical bridging (i.e., efficacy and safety) between once daily and twice daily dosing of metformin. Refer specific cases with additional details to section 3.1 of this review.

The applicant conducted two pivotal BE studies because there are two proposed strengths for JENTADUETO® XR under fasted or fed conditions (Table 1).

Table 1 Overview of pivotal bridging studies for linagliptin/metformin FDC XR

Study No. Report No.	Objective and description	Study part, meal status	Test (FDC dose tested (mg))	Reference (co-administration dose tested (mg))
1288.9 C02895304	Bioequivalence, single-dose	1, fasted	Lina 5/met XR 1000	Lina 5 + 2x met XR 500
		2, fed	Lina 5/met XR 1000	Lina 5 + 2x met XR 500
1288.11 C02728714	Bioequivalence, single-dose	1, fasted	2x(lina 2.5/met XR 1000)	Lina 5 + 4x met XR 500
		2, fed	2x(lina 2.5/met XR 1000)	Lina 5 + 4x met XR 500

The BE was demonstrated for both strengths of JENTADUETO® XR referencing corresponding co-administration of TRADJENTA® and GLUMETZA® under both fasted and fed conations (Table 2).

Table 2 Statistical evaluations for bioequivalence in: least square geometric mean ratios (FDC/co-administration) (90% CI)

Study 1288.9 (dose level investigated: 5/1000 mg)

	Part 1 (fasted conditions)	Part 2 (fed conditions)
Linagliptin		
AUC_{0-72}	100.4 (96.6, 104.3)%	94.7 (88.7, 101.1)%
C_{max}	108.1 (99.0, 118.0)%	98.2 (94.1, 102.6)%
Metformin		
AUC_{0-72}	100.0 (93.0, 107.5)%	97.0 (92.2, 101.9)%
C_{max}	99.8 (92.5, 107.6)%	99.0 (95.0, 103.2)%

Study 1288.11 (dose level investigated: 5/2000 mg)

	Part 1 (fasted conditions)	Part 2 (fed conditions)
Linagliptin		
AUC_{0-72}	103.7 (100.7, 106.7)%	101.6 (93.7, 110.2)%
C_{max}	114.6 (107.7, 121.9)%	98.3 (86.5, 111.6)%
Metformin		
AUC_{0-72}	96.5 (91.2, 102.0)%	97.8 (90.5, 105.6)%
C_{max}	98.0 (92.0, 104.3)%	105.9 (96.7, 115.9)%

In conclusion, the clinical pharmacology information of JENTADUETO® XR supports the recommendation of approval as follows:

- The pivotal BE study results are acceptable from the clinical pharmacology perspective
- The clinical comparability between metformin twice daily (GLUCOPHAGE®) and once daily (GLUMETZA®) was shown in the original NDA for GLUMETZA®, the metformin XR reference product for JENTADUETO® XR
- The efficacy and safety of co-administration between linagliptin and metformin twice daily (GLUCOPHAGE®) has been adequately demonstrated as add-on (TRADJENTA®) and initial (JENTADUETO®) therapy

2.2 Summary of Labeling Recommendations

To be updated

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

The JENTADUETO® XR consists of a metformin HCl extended release tablet core that is film coated with immediate-release linagliptin (Figure 1). Components and composition of formulations are summarized in Appendix.

Figure 1 Schematic of the tablet and photographs of JENTADUETO® XR

General regulatory background

A typical clinical development for a FDC product of a DPP-4 inhibitor and metformin is based on the pivotal BE bridging of a FDC referencing co-administration of each products of active ingredients, and efficacy and safety of a DPP-4 inhibitor for add-on to metformin BID, which is typically available from the original NDA for a DPP-4 inhibitor (Table 2). Meal conditions for a FDC administration is followed by those of metformin reference product as the meal condition for a DPP-4 inhibitor is generally not limited (Table 2).

For FDC XR development, the pivotal BE bridging of a FDC XR referencing co-administration of a DPP-4 inhibitor and metformin XR, and efficacy and safety of co-administration of a DPP-4 inhibitor and metformin BID with clinical comparability between once daily and twice daily of metformin from metformin XR reference product. Currently three approved metformin XR products are available with different extended-release mechanisms and clinical bridging information (Table 3).

Product specific regulatory background

The efficacy and safety of linagliptin 5 mg once daily for add-on to a stable metformin twice daily with GLUCOPHAGE® was shown in the original NDA for TRADJENTA® (NDA 201280). Further, in the original NDA for JENTADUETO® (NDA 201281) the efficacy and safety as the initial therapy following co-administration of linagliptin and metformin (GLUCOPHAGE®) twice daily was shown and the pivotal BE of FDC referencing co-administration of TRADJENTA® and GLUCOPHAGE® was demonstrated. The efficacy and safety of GLUMETZA®(metformin XR) once daily was comparable to that of GLUCOPHAGE® (metformin IR) twice daily with in the original NDA for GLUMETZA® (NDA 021748).

The BE of JENTADUETO® XR was demonstrated referencing co-administration of TRADJENTA® and GLUMETZA®. Therefore, there is sufficient bridging information for JENTADUETO® XR to refer pertinent labeling from TRADJENTA®, GLUMETZA® and JENTADUETO® (Figure 2).

Table 3 Currently available FDC products between a DPP-4 inhibitor and metformin, and the pivotal bridging information with labeling related to meal conditions for administration (yellow highlight indicates a FDC XR)

Combination Products[1]	Referencing products	Approved Tablet Strengths	Major bridging information	Meal conditions
JANUMET® (sitagliptin / metformin IR) AP: 3/30/2007	JANUVIA® (sitagliptin) + APOTEX (generic metformin)	50/500, 50/1000	BE under fasting conditions	With meals
KOMBIGLYZE® XR (saxagliptin / metformin XR) 11/5/2010	ONGLYZA® (saxaglitpin) + GLUCOPAHGE® XR	5/500, 5/1000, 2.5/1000	BE + food effect (5/500 under fast or low fat, 5+500) BE (5/1000 under low fat)	With the evening meal
JANUMET XR® (sitagliptin / metformin XR) AP: 2/2/2012	JANUVIA® (sitagliptin) + GLUMETZA®	50/500, 50/1000, 100/1000	• BE (50/500, 100/1000; 2x50/500, 50+500, 100+1000) under high fat breakfast • Food effect study (50/1000, JANUMET® (50/1000)) • BE (50/500, 50/850; 50/1000 FMI vs. JANUVIA® + GLUCOPAHGE® EU) under fasting conditions • other studies (PD, MD)	With a meal preferably in the evening
JENTADUETO® (linagliptin / metformin IR) AP: 1/30/2012	TRADDENTA® (linagliptin) + GLUCOPHAGE®	2.5/500, 2.5/850, 2.5/1000	BE under fasting condition	With meals
KAZANO® (alogliptin / metformin IR) AP: 1/25/2013	NESINA® (alogliptin) + GLUCOPHAGE®	12.5/500, 12.5/1000	• BE under fasting condition • Food effect	With food

[1] chronological order by Approval (AP) date

Table 4 Currently available metformin XR products and the pivotal bridging information with labeling related to meal conditions for administration

Products[1]	Referencing product	Strength	Major bridging information	D&A (starting and maximum dose, meal condition) [2]
GLUCOPAHGE® XR AP: 10/13/2000	GLUCOPAHGE®	500, 750	Dose-Response (two Phase 3 studies with 12-16 weeks) Similar efficacy to GLUCOPAHGE® (24 weeks)	500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal
FORTAMET®[3] AP: 4/28/2004	GLUCOPAHGE®	500, 1000	Close efficacy to GLUCOPAHGE® (three Phase 3 studies)	Start 1000 mg although 500 may be utilized, the maximum recommend daily dose up to 2500 mg with the evening meal
GLUMETZA®[4] AP: 6/3/2005	GLUCOPAHGE®	500, 1000	Approximately the same as of GLUCOPAHGE® (two Phase 3 studies)	Initiate with 500 mg daily, not exceeding the maximum recommend daily dose of 2000 mg with the evening meal

[1] Chronological order by Approval (AP) date
[2] Dosage and administration
[3] It is formulated using the patented single-composition osmotic technology
[4] It is formulated to gradually release metformin to the upper gastrointestinal tract

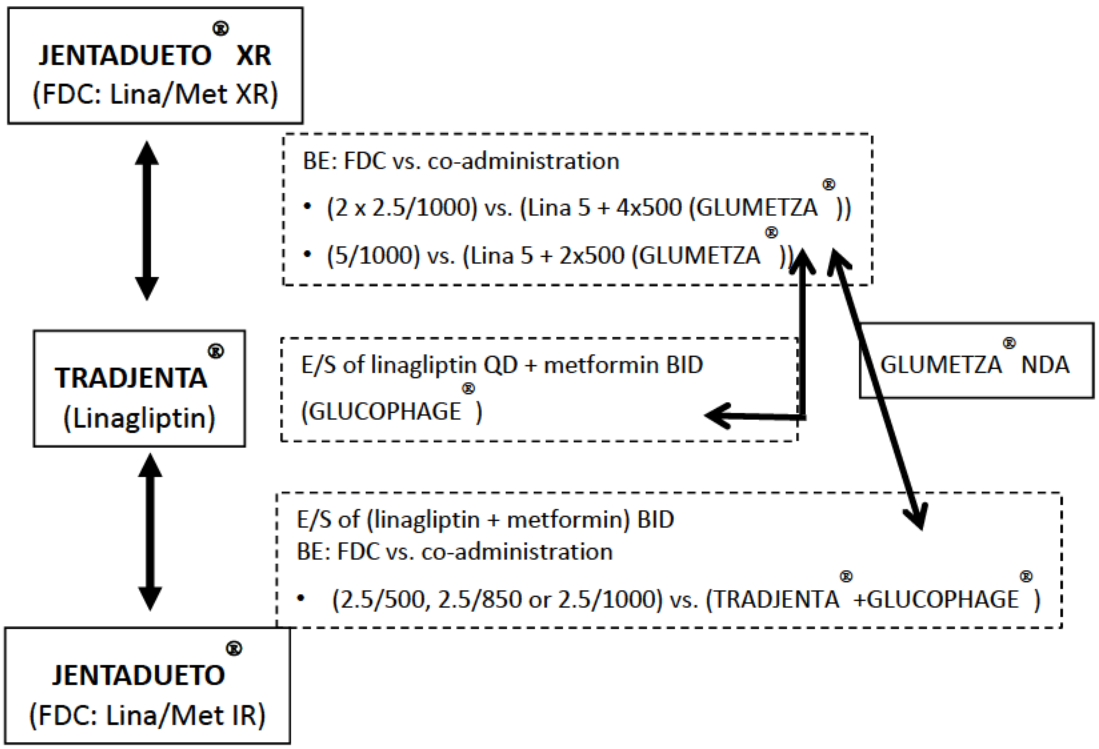


Figure 2 Schematic summary of pivotal bridging information supporting JENTADUETO® XR

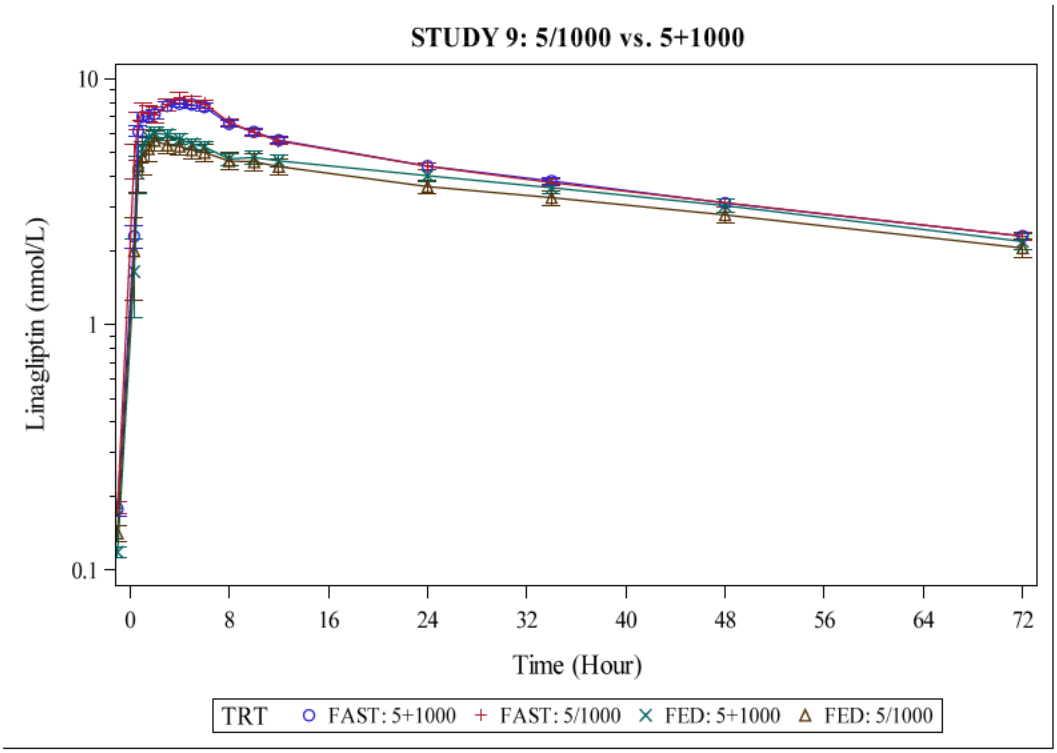
3.2 Clinical Pharmacology Review Questions

3.2.1 Does the available clinical pharmacology information provide the pivotal bridging?

Yes, because the BE of JENTADUETO® XR was demonstrated referencing co-administration of TRADJENTA® and GLUMETZA® in two different dose levels (i.e., 5 mg linagliptin/1000 mg metformin XR and 5 mg linagliptin/2000 mg metformin XR)

The BE of linagliptin and metformin following JENTADUETO® XR (one tablet of 5/1000) was assessed referencing those of co-administration of TRADJENTA® (one tablet 5 mg) and GLUMETZA® (two tablets 500 mg) under fasted and fed (high-fat) conditions in a two-way crossover trial with healthy volunteers (Study 1288.0009).

Plasma concentration of linagliptin and metformin – time profiles by treatments are shown in Figure 3 and pharmacokinetic parameters are summarized in Table 5. The FDC of 5 mg linagliptin/1000 mg metformin XR is bioequivalent to co-administration of single tablet 5 mg linagliptin and 1000 mg metformin XR (two tablets 500 mg) both under fasted and fed conditions (Table 2).



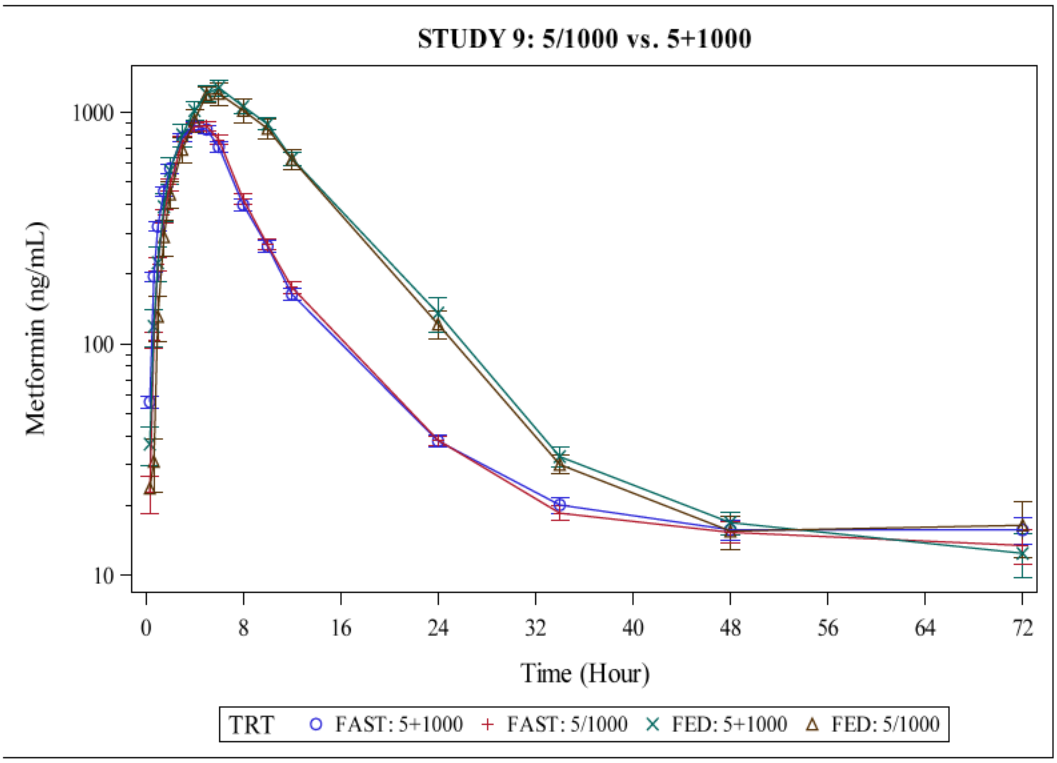


Figure 3 Mean (SE) linagliptin (left) or metformin (right) concentration – time profiles by treatments

Table 5 Descriptive statistics of PK parameters in Study 1288.9

	Part 1 (fasted conditions)		Part 2 (fed conditions)	
	FDC	**Co-administration**	**FDC**	**Co-administration**
Linagliptin, N analyzed	52	52	14	15
AUC_{0-72}, gMean (gCV) [nmol·h/L]	288 (24.1%)	287 (23.9%)	226 (41.2%)	252 (23.7%)
C_{max}, gMean (gCV) [nmol/L]	9.54 (36.1%)	8.83 (28.1%)	5.76 (49.6%)	6.30 (23.4%)
$AUC_{0-\infty}$, gMean (gCV) [nmol·h/L]	460 (31.9%)	461 (27.8%)	392 (59.8%)	419 (33.5%)
t_{max}, median (min, max) [h]	3.00 (0.333, 6.05)	4.00 (0.667, 6.02)	2.00 (0.333, 24.0)	2.00 (0.683, 5.00)
$t_{1/2}$, gMean (gCV) [h]	52.5 (24.1%)	53.1 (21.8%)	55.7 (44.9%)	52.7 (30.3%)
Metformin, N analyzed	52	52	14	15
AUC_{0-tz}, gMean (gCV) [ng·h/mL]	7150 (26.7%)	7150 (31.9%)	11000 (167%)	14800 (23.2%)
C_{max}, gMean (gCV) [ng/mL]	924 (31.0%)	926 (30.9%)	928 (183%)	1260 (26.7%)
$AUC_{0-\infty}$, gMean (gCV) [ng·h/mL]	7540 (28.7%)	7610 (32.4%)	15 200 (22.7%)[1]	15 100 (23.5%)
t_{max}, median (min, max) [h]	4.00 (3.00, 6.00)	4.00 (2.00, 6.02)	6.00 (5.00, 12.0)	6.00 (5.00, 8.00)
t_z, median (min, max) [h]	48.0 (24.0, 72.0)	48.0 (24.0, 72.0)	48.0 (24.0, 72.0)	48.0 (48.0, 72.0)
$t_{1/2}$, gMean (gCV) [h]	13.5 (108%)	15.1 (109%)	12.8 (116%)[1]	13.0 (80.0%)

gCV: geometric coefficient of variation between subjects
1 N analyzed=13

The bioequivalence of linagliptin and metformin following JENTADUETO® XR (two tablets of 2.5/1000) was assessed referencing those of co-administration of TRADJENTA® (one tablet 5 mg) and GLUMETZA® (four tablets 500 mg) under fasted and fed (high-fat) conditions in a two-way crossover trial with healthy volunteers (Study 1288.0011).

Plasma concentration of linagliptin and metformin – time profiles by treatments are shown in Figure 4 and pharmacokinetic parameters are summarized in Table 6. The FDC at dose level of 5 mg linagliptin/2000 mg metformin XR is bioequivalent to co-administration of 5 mg linagliptin (single tablet 5 mg) and 2000 mg metformin XR (four tablets 500 mg) both under fasted and fed conditions (Table 2).

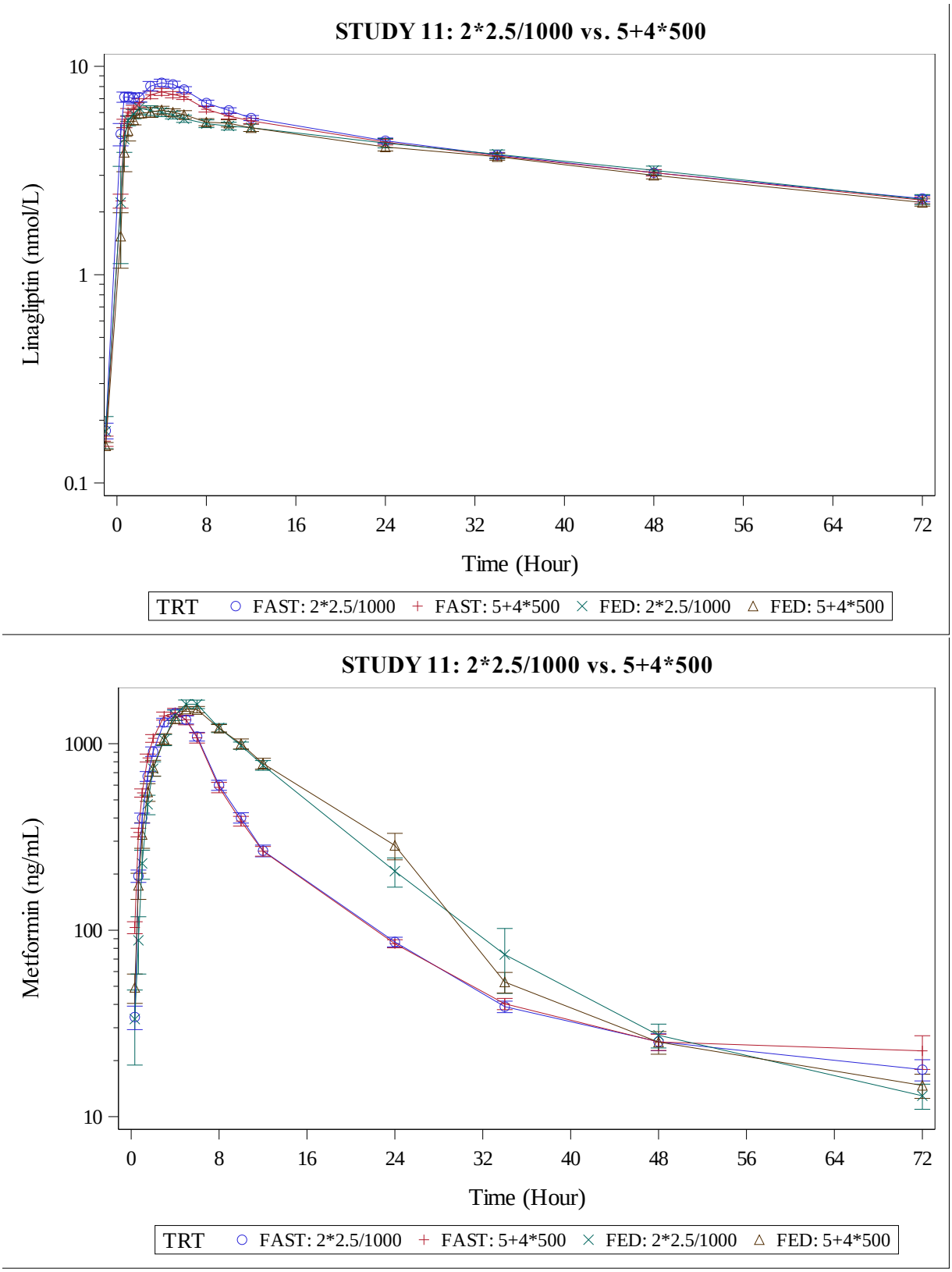


Figure 4 Mean (SE) linagliptin (left) or metformin (right) concentration – time profiles by treatments

Table 6 Descriptive statistics of PK parameters in Study 1288.11

	Part 1 (fasted conditions)		Part 2 (fed conditions)	
	FDC	Free combination	FDC	Free combination
Linagliptin, N analyzed	57	55	15	16
AUC_{0-72}, gMean (gCV) [nmol·h/L]	289 (22.4%)	279 (23.4%)	270 (18.5%)	265 (14.1%)
C_{max}, gMean (gCV) [nmol/L]	9.49 (36.2%)	8.19 (28.2%)	6.61 (28.7%)	6.73 (19.9%)
$AUC_{0-\infty}$, gMean (gCV) [nmol·h/L]	475 (29.4%)	458 (30.6%)	452 (22.1%)	446 (16.5%)
t_{max}, median (min, max) [h]	3.00 (0.333, 6.02)	4.00 (0.667, 12.0)	2.00 (0.333, 5.03)	3.51 (0.667, 5.00)
$t_{1/2}$, gMean (gCV) [h]	55.8 (25.0%)	54.7 (24.8%)	54.1 (23.7%)	55.9 (19.5%)
Metformin, N analyzed	56	56	15	15
AUC_{0-tz}, gMean (gCV) [ng·h/mL]	11 600 (35.9%)	12 000 (31.9%)	19 800 (16.3%)	20 300 (17.1%)
C_{max}, gMean (gCV) [ng/mL]	1490 (33.2%)[1]	1520 (33.1%)	1650 (21.0%)	1570 (12.9%)
$AUC_{0-\infty}$, gMean (gCV) [ng·h/mL]	12 100 (37.3%)	12 700 (33.9%)	20 200 (16.7%)	20 600 (17.8%)
t_{max}, median (min, max) [h]	4.00 (2.00, 5.03) [1]	3.51 (1.50, 5.02)	6.00 (5.00, 8.00)	5.00 (4.00, 6.00)
t_z, median (min, max) [h]	48.0 (12.0, 72.1)	48.0 (34.0, 72.1)	72.0 (48.0, 72.1)	72.0 (48.0, 72.0)
$t_{1/2}$, gMean (gCV) [h]	13.7 (93.1%)	14.8 (88.3%)	13.1 (71.8%)	12.3 (63.3%)

gCV: geometric coefficient of variation between subjects
[1] N analyzed=57

GLUMETZA® labeling indicates that high-fat and low fat meals increase metformin AUC by 73% and 38%, respectively, compared to those of fasting. It seems that high-fat meal increase similar metformin AUC from JENTADUETO® XR, and it further support that JENTADUETO® XR can refer the same labeling for meal condition related to dosing administration as that of GLUMETZA®.

Plasma concentrations of linagliptin and metformin were measured using validated HPLC-MS/MS methods. Accuracy and precision data of quality control samples are shown in Table 7. The Office of Study Integrity and Surveillance recommends that the bioanalytical data be accepted for review (refer details to the review by Dr. Li-Hong Paul Yeh dated 3/15/2016).

Table 7 accuracy and precision data of quality control samples

Analyte	Label	Concentration [1]	N	Deviation [%] [2]	CV [%]
Linagliptin (BI 1356)	LoQC	0.300	60	-1.7	2.8
	MeQC	2.0	60	0.0	2.3
	HiQC	16.0	60	-1.9	2.2
Metformin	QC.LOW	10.0	50	0.00	5.01
	QC.MID	1000	50	2.00	2.80
	QC.HIGH	2000	50	1.50	3.49

[1] [nmol/L] for linagliptin and [ng/mL] for metformin
[2] based on residual standard deviation for linagliptin, and on residual standard error for metformin

4 Appendices

4.1 Components and composition of JENTADUETO® XR

Ingredient	2.5 mg / 1000 mg [mg / tablet]	5 mg / 1000 mg [mg / tablet]	Function	Reference to Standards
(b) (4)				

4.2 Synopsis: Study 1288.9

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005142-11	
BI Investigational Product: Linagliptin (BI1356)/metformin extended release (fixed dose combination)		**Page:** 1 of 5	
Report Date: 13 Feb 2015	**Trial No. / Doc. No.:** 1288.9 / c02895304-01	**Dates of Trial:** 13 May 2014 - 31 Jul 2014	**Date of Revision:** Not applicable

Title of Trial:	Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised, single dose, two-way crossover trial)
Principal Investigator:	Dr Fabian Müller
Trial Sites:	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine and Clinical Pharmacology, Human Pharmacology Centre, Birkendorfer Str. 65, Biberach/Riss, Germany
Publications:	Data from this trial have not been published at the time of this clinical trial report.
Clinical Phase:	I
Objectives:	The objective was to establish the bioequivalence of linagliptin/metformin extended release (XR) fixed dose combination (FDC) tablets versus the free combination of linagliptin tablets and metformin XR tablets under fasted (Part 1) and fed (Part 2) conditions.
Methodology:	This was a randomised, open-label, single-dose, 2-way crossover trial with 2 individual study parts: Part 1: one 5 mg linagliptin/1000 mg metformin XR FDC tablet versus the free combination (1 tablet 5 mg linagliptin and 2 tablets 500 mg metformin XR) under fasted conditions Part 2: one 5 mg linagliptin/1000 mg metformin XR FDC tablet versus the free combination (1 tablet 5 mg linagliptin and 2 tablets 500 mg metformin XR) under fed conditions
No. of Subjects:	
Planned:	Entered: 68 (52 under fasted conditions; 16 under fed conditions)
Actual:	Entered: 68 (52 under fasted conditions; 16 under fed conditions) Part 1 (fasted conditions): FDC: Treated: 52 Analysed (for primary endpoints): 52 Free combination: Treated: 52 Analysed (for primary endpoints): 52 Part 2 (fed conditions): FDC: Treated: 14 Analysed (for primary endpoints): 14 Free combination: Treated: 15 Analysed (for primary endpoints): 15

Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male and female subjects, age 18 to 55 years, body mass index (BMI) 18.5 to 29.9 kg/m^2
BI Investigational Product:	5 mg linagliptin/1000 mg metformin XR FDC tablet
Dose:	5 mg linagliptin/1000 mg metformin XR (given as 1 FDC tablet)
Mode of Admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study part and after a high-fat, high-calorie meal for the fed study part
Batch No.:	B141000803
Comparator Products:	Comparator product 1: Tradjenta® (5 mg linagliptin tablet) Comparator product 2: Glumetza® (500 mg metformin XR tablet)
Dose:	5 mg linagliptin and 1000 mg metformin XR (given as 1 tablet 5 mg linagliptin and 2 tablets 500 mg metformin XR)
Mode of Admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study part and after a high-fat, high-calorie meal for the fed study part
Batch No.:	Tradjenta® 5 mg: B141000802 Glumetza® 500 mg: B141000801
Duration of Treatment:	Single dose for each treatment
Criteria for Evaluation:	
Clinical Pharmacology:	The following pharmacokinetic parameters were evaluated as primary endpoints: AUC_{0-72} and C_{max} for linagliptin, AUC_{0-tz} and C_{max} for metformin The following pharmacokinetic parameters were evaluated as secondary endpoints: $AUC_{0-\infty}$ for both linagliptin and metformin
Safety:	The evaluation of safety was based on: adverse events (including clinically relevant findings from the physical examination), safety laboratory tests, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG)

Statistical Methods:	The assessment of bioequivalence was based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (FDC/free combination) for the primary endpoints using an acceptance range of 80.00 to 125.00%. 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 logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints. No interim analysis was performed.
SUMMARY - CONCLUSIONS:	
Trial Subjects and Compliance with Trial Protocol:	A total of 68 healthy volunteers participated in the study. Fifty-two subjects participated in Part 1, all of whom completed the study as planned. Twenty-three study participants were male (44.2%) and 29 were female (55.8%). Age ranged from 19 to 54 years (mean: 34.7 years, standard deviation [SD]: 10.4 years), and BMI ranged from 19.1 to 29.1 kg/m^2 (mean: 23.93 kg/m^2, SD: 2.47 kg/m^2). Sixteen subjects participated in Part 2, three of whom prematurely discontinued study participation. Two subjects discontinued due to adverse events: 1 subject after having been treated with the free combination and 1 subject after having been treated with the FDC in the first treatment period. One subject withdrew consent after having been treated with the free combination. Six study participants were male (37.5%) and 10 were female (62.5%). Age ranged from 18 to 53 years (mean: 36.1 years, SD: 11.9 years), and BMI ranged from 19.6 to 29.1 kg/m^2 (mean: 24.54 kg/m^2, SD: 2.96 kg/m^2). All 68 subjects in this study were White. No relevant medical history or baseline conditions were reported for any of the participating subjects. All subjects were treated with at least 1 dose of study medication. No important protocol violations were reported.
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 in each study part. The adjusted gMean values, the adjusted gMean ratios (FDC to free combination), 2-sided 90% CIs, and intra-subject geometric coefficient of variation (gCV) values for all primary and secondary endpoints are summarised in Table 1 below.

Clinical Pharmacology Results (cont.):

For each study part, the adjusted gMean ratios FDC to free combination for the primary endpoints (AUC_{0-72} and C_{max} of linagliptin and AUC_{0-tz} and C_{max} of metformin) were close to 100%, with their corresponding 90% CIs within the pre-defined acceptance range for bioequivalence of 80.00 to 125.00%. The adjusted gMean ratios for the secondary endpoint, $AUC_{0-\infty}$ of linagliptin and metformin, were close to 100%, with their corresponding 90% CIs within the acceptance range for bioequivalence, except for $AUC_{0-\infty}$ of linagliptin under fed conditions, for which the lower limit of the 90% CI was outside the bioequivalence limit.

Table 1: Analysis of bioequivalence of linagliptin and metformin after administration of 5 mg linagliptin and 1000 mg metformin XR as FDC or free combination

Analyte Parameter	Adjusted gMean FDC	Adjusted gMean free combination	Adjusted gMean ratio FDC/free combination [%]	90% CI (upper limit, lower limit) [%]	Intra-individual gCV [%]
Part 1 (fasted conditions)					
Linagliptin (FDC N=52, free combination N=52)					
AUC_{0-72} [nmol·h/L]	288	287	100.4	(96.6, 104.3)	11.8
C_{max} [nmol/L]	9.54	8.83	108.1	(99.0, 118.0)	27.1
$AUC_{0-\infty}$ [nmol·h/L]	460	461	99.7	(95.2, 104.5)	14.3
Metformin (FDC N=52, free combination N=52)					
AUC_{0-tz} [ng·h/mL]	7146	7147	100.0	(93.0, 107.5)	22.2
C_{max} [ng/mL]	924	926	99.8	(92.5, 107.6)	23.4
$AUC_{0-\infty}$ [ng·h/mL]	7540	7608	99.1	(92.4, 106.4)	21.7
Part 2 (fed conditions)					
Linagliptin (FDC N=14, free combination N=15)					
AUC_{0-72} [nmol·h/L]	222	234	94.7	(88.7, 101.1)	9.2
C_{max} [nmol/L]	5.69	5.79	98.2	(94.1, 102.6)	6.1
$AUC_{0-\infty}$ [nmol·h/L]	387	398	97.4	(77.1, 123.0)	32.4
Metformin (FDC N=14, free combination N=15)[1]					
AUC_{0-tz} [ng·h/mL]	10 980	11 326	97.0	(92.2, 101.9)	7.1
C_{max} [ng/mL]	938	947	99.0	(95.0, 103.2)	5.9
$AUC_{0-\infty}$ [ng·h/mL][1]	14 774	15 047	98.2	(93.3, 103.3)	7.2

[1] One subject excluded from $AUC_{0-\infty}$ calculation for the FDC (FDC N=13, free combination N=15)

Safety Results:	During the treatment periods of the 2 study parts, adverse events (AEs) were reported for a total of 26 subjects (38.2%). No deaths, protocol-specified adverse events of special interest (AESIs), or other significant AEs according to ICH E3 were reported in this study. All AEs had either resolved by the end of the study or had been sufficiently followed-up. There were no clinically relevant findings with respect to safety laboratory tests, vital signs, or ECG. In Part 1, AEs were reported for 10 of 52 subjects (19.2%) during the treatment period with the free combination and for 13 of 52 subjects (25.0%) during the treatment period with the FDC tablet. All AEs were of mild or moderate intensity; no serious adverse events (SAEs) were reported in this study part. Four subjects (7.7%) reported AEs that were assessed as drug-related by the investigator (headache and diarrhoea). AEs reported for more than 1 subject in this study part at the preferred term level were headache (7 subjects, 13.5%), diarrhoea (4 subjects, 7.7%), dizziness, rhinitis, nasopharyngitis, and back pain (reported for 2 subjects each, 3.8%). In Part 2, AEs were reported for 5 of 15 subjects (33.3%) during the treatment period with the free combination and for 4 of 14 subjects (28.6%) during the treatment period with the FDC tablet. Two subjects were reported with SAEs after treatment with the free combination: 1 subject had a fall and 1 subject had a road traffic accident, 26 and 15 days after the day of drug intake, respectively. The SAEs were severe in intensity; all other AEs were of mild or moderate intensity. One subject terminated the study prematurely after treatment with the FDC due to a suspected drug-induced allergic skin reaction (rash). Five subjects (31.3%) reported AEs that were assessed as drug-related by the investigator (headache, decreased appetite, vertigo, diarrhoea, abdominal discomfort, and rash). The most frequently reported AE (reported for more than 1 subject) in this study part at the preferred term level was headache (2 subjects, 12.5%).
Conclusions:	The fixed-dose combination tablet of 5 mg linagliptin/1000 mg metformin XR was bioequivalent to single tablets 5 mg linagliptin and 1000 mg metformin XR administered together, both under fasted and fed conditions. All adjusted geometric mean ratios FDC/free combination for AUC_{0-72} and C_{max} of linagliptin, and AUC_{0-tz} and C_{max} of metformin were close to 100% with their corresponding 90% CIs within the pre-defined acceptance range of 80.00 to 125.00%. All treatments investigated in this study were safe and well tolerated in healthy male and female subjects.

4.3 Synopsis: Study 1288.11

Name of Company: Boehringer Ingelheim		Synopsis	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-005144-28	
BI Investigational Product: Linagliptin / metformin extended release (fixed dose combination)		**Page:** 1 of 6	
Report Date: 19 FEB 2015	**Trial No. / Doc. No.:** 1288.11 / c02728714-01	**Dates of Trial:** 24 Apr 2014 – 11 Jul 2014	**Date of Revision:** Not applicable

Title of Trial:	Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (2.5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised, single dose, two-way crossover trial)
Principal Investigator:	Tobias Brand
Trial Site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine and Clinical Pharmacology, Human Pharmacology Centre, Birkendorfer Str. 65, Biberach/Riss, Germany
Publications:	Data from this trial have not been published at the time of this clinical trial report.
Clinical Phase:	I
Objectives:	The objective was to establish the bioequivalence of linagliptin/metformin extended release (XR) fixed dose combination (FDC) tablets versus the free combination of linagliptin tablets and metformin XR tablets under fasted (Part 1) and fed (Part 2) conditions.
Methodology:	This was a randomised, open-label, single-dose, 2-way crossover trial with 2 individual study parts: Part 1: two 2.5 mg linagliptin/1000 mg metformin XR FDC tablets versus the free combination (1 tablet 5 mg linagliptin and 4 tablets 500 mg metformin XR) under fasted conditions Part 2: two 2.5 mg linagliptin/1000 mg metformin XR FDC tablets versus the free combination (1 tablet 5 mg linagliptin and 4 tablets 500 mg metformin XR) under fed conditions
No. of Subjects:	
Planned:	Entered: 74 (58 under fasted conditions; 16 under fed conditions)
Actual:	Entered: 74 (58 under fasted conditions; 16 under fed conditions) Part 1 (fasted conditions): FDC: Treated: 58 Analysed (for primary endpoints): 57 (linagliptin), 56 (metformin) Free combination: Treated: 56 Analysed (for primary endpoints): 55 (linagliptin), 56 (metformin)

No. of Subjects (cont.):	Part 2 (fed conditions): FDC: Treated: 16 Analysed (for primary endpoints): 15 (both analytes) Free combination: Treated: 16 Analysed (for primary endpoints): 16 (linagliptin), 15 (metformin)
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male and female subjects, age 18 to 55 years, body mass index (BMI) 18.5 to 29.9 kg/m^2
BI Investigational Product:	2.5 mg linagliptin/1000 mg metformin XR FDC tablet
Dose:	5 mg linagliptin and 2000 mg metformin XR (given as 2 FDC tablets)
Mode of Admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study part and after a high-fat, high-calorie meal for the fed study part
Batch No.:	B141000640 (3117868R)
Comparator Products:	Comparator product 1: Tradjenta® (5 mg linagliptin tablet) Comparator product 2: Glumetza® (500 mg metformin XR tablet)
Dose:	5 mg linagliptin and 2000 mg metformin XR (given as 1 tablet 5 mg linagliptin and 4 tablets 500 mg metformin XR)
Mode of Admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h for the fasted study part and after a high-fat, high-calorie meal for the fed study part
Batch Nos.:	Tradjenta® 5 mg: B141000006 (361463C) Glumetza® 500 mg: B131003751 (MTBT9461)
Duration of Treatment:	Single dose for each treatment
Criteria for Evaluation:	
Clinical Pharmacology:	The following pharmacokinetic parameters were evaluated as primary endpoints: AUC_{0-72} and C_{max} for linagliptin, AUC_{0-tz} and C_{max} for metformin The following pharmacokinetic parameters were evaluated as secondary endpoints: $AUC_{0-\infty}$ for both linagliptin and metformin
Safety:	The evaluation of safety was based on: monitoring of adverse events (AEs; including clinically relevant findings from the physical examination), safety laboratory tests, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG).

Statistical Methods:	The assessment of bioequivalence was based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (FDC/free combination) for the primary endpoints using an acceptance range of 80.00 to 125.00%. 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 logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints. No interim analysis was performed.
SUMMARY - CONCLUSIONS:	
Trial Subjects and Compliance with Trial Protocol:	A total of 74 healthy subjects were entered into the study and treated, 58 in Part 1 (fasted conditions) and 16 in Part 2 (fed conditions). Seventy-two subjects completed the trial according to protocol, 56 in Part 1 and 16 in Part 2. Two subjects participating in Part 1 withdrew their consent and prematurely discontinued trial participation. Both subjects were treated with the FDC in the first treatment period but did not receive the free combination in the second treatment period. There were no important protocol violations in this trial. Of the 58 subjects entered in Part 1, 20 (34.5%) were male and 38 (65.5%) were female. All subjects were White. The age (mean and standard deviation [SD]) of the subjects was 33.1 (9.8) years and the BMI (mean and SD) was 23.38 (2.71) kg/m^2. Of the 16 subjects entered in Part 2, 9 (56.3%) were male and 7 (43.8%) were female. One subject was Black (6.3%); 15 subjects were White (93.8%). The age of the subjects was 32.6 (8.2) years and the BMI was 24.21 (2.10) kg/m^2.
Clinical Pharmacology Results:	In both study parts, geometric mean (gMean) plasma concentration-time profiles and pharmacokinetic parameters of linagliptin and metformin were similar for the FDC and the free combination. The adjusted gMean values, the adjusted gMean ratios FDC/free combination, 2-sided 90% CIs, and intrasubject geometric coefficient of variation (gCV) values for all primary and secondary endpoints are summarised in Table 1 below. In both study parts, gMean ratios FDC/free combination for the primary endpoints AUC_{0-72} and C_{max} of linagliptin and AUC_{0-tz} and C_{max} of metformin and the corresponding 2-sided 90% CIs were

Clinical Pharmacology Results (cont.):

within the pre-defined acceptance range of 80.00 to 125.00%. Thus, bioequivalence was established between the FDC and the free combination under fasted and fed conditions. For the secondary endpoints $AUC_{0-\infty}$ of linagliptin and $AUC_{0-\infty}$ of metformin, gMean ratios FDC/free combination and 2-sided 90% CIs were also within the acceptance range of 80.00 to 125.00% under fasted and fed conditions.

Table 1: Analysis of bioequivalence of linagliptin and metformin after administration of 5 mg linagliptin and 2000 mg metformin XR as 2 FDC tablets (2.5 mg/1000 mg) or the free combination under fasted and fed conditions

Analyte Parameter	Adjusted gMean FDC	Adjusted gMean free combination	Adjusted gMean ratio FDC/free combination [%]	Two-sided 90% CI (upper limit, lower limit) [%]	Intra-individual gCV [%]
Part 1 (fasted conditions)					
Linagliptin (FDC N=57, free combination N=55)					
AUC_{0-72} [nmol·h/L]	289	278	103.7	(100.7, 106.7)	9.1
C_{max} [nmol/L]	9.48	8.27	114.6	(107.7, 121.9)	19.6
$AUC_{0-\infty}$ [nmol·h/L]	474	458	103.5	(98.4, 108.8)	15.8
Metformin (FDC N=56[1], free combination N=56)					
AUC_{0-tz} [ng·h/mL]	11 601	12 028	96.5	(91.2, 102.0)	17.6
C_{max} [ng/mL]	1486	1517	98.0	(92.0, 104.3)	19.9
$AUC_{0-\infty}$ [ng·h/mL]	12 162	12 737	95.5	(89.7, 101.6)	19.7
Part 2 (fed conditions)					
Linagliptin (FDC N=15, free combination N=16)					
AUC_{0-72} [nmol·h/L]	269	265	101.6	(93.7, 110.2)	12.7
C_{max} [nmol/L]	6.61	6.73	98.3	(86.5, 111.6)	20.1
$AUC_{0-\infty}$ [nmol·h/L]	452	446	101.4	(91.1, 112.7)	16.7
Metformin (FDC N=15, free combination N=15)					
AUC_{0-tz} [ng·h/mL]	19 953	20 411	97.8	(90.5, 105.6)	11.7
C_{max} [ng/mL]	1663	1571	105.9	(96.7, 115.9)	13.8
$AUC_{0-\infty}$ [ng·h/mL]	20 346	20 721	98.2	(90.7, 106.3)	11.9

[1] C_{max}: N=57

Safety Results:	No serious AEs, no protocol-specified AEs of special interest, and no other significant AEs according to ICH E3 occurred in this trial, and no subject discontinued the trial due to an AE. All subjects had recovered from their AEs by the end of the trial. Safety laboratory tests and the evaluation of vital signs and ECG revealed no clinically significant findings in this trial. *Part 1 (fasted conditions)* Adverse events were reported for 39 subjects (67.2%). Twenty-eight subjects (50.0%) reported AEs in the treatment period with the free combination and 26 subjects (44.8%) reported AEs in the treatment period with the FDC. Adverse events reported for more than 1 subject were headache (16 subjects, 27.6%), diarrhoea (8 subjects, 13.8%), abdominal pain (7 subjects, 12.1%), nausea (6 subjects, 10.3%), dizziness (5 subjects, 8.6%), abdominal discomfort (4 subjects, 6.9%), nasopharyngitis (3 subjects, 5.2%), vessel puncture site haematoma (3 subjects, 5.2%), and otitis externa (2 subjects, 3.4%). Twenty-seven subjects (46.6%) reported AEs that were assessed by the investigator as drug-related. The most frequent drug-related AEs were gastrointestinal disorders (17 subjects, 29.3%). One subject reported an AE of severe intensity (headache) in the treatment period with the FDC; all other AEs were of mild or moderate intensity. *Part 2 (fed conditions)* Adverse events were reported for 10 subjects (62.5%). Eight subjects (50.0%) reported AEs in the treatment period with the free combination and 5 subjects (31.3%) reported AEs in the treatment period with the FDC. Adverse events reported for more than 1 subject were diarrhoea (5 subjects, 31.3%), headache (4 subjects, 25.0%), abdominal pain, nausea, and vomiting (each reported for 2 subjects, 12.5%). Seven subjects (43.8%) reported AEs that were assessed by the investigator as drug-related. The most frequent drug-related AEs were gastrointestinal disorders (6 subjects, 37.5%). All AEs in this study part were of mild or moderate intensity.

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/s/

SANG M CHUNG
04/27/2016

MANOJ KHURANA
04/27/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208026	**SDN**	
Applicant	Boehringer Ingelheim	**Submission Date**	July 27, 2015
Generic Name	Linagliptin/Metformin HCl XR FDC	**Brand Name**	Jentadueto XR
Drug Class			
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate		
Dosage Regimen	Once daily		
Dosage Form	Tablet	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	DMEP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Sang M Chung	Manoj Khurana
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	9/9/2015	**74-Day Letter Date**	10/9/2015
Review Due Date	4/20/2016	**PDUFA Goal Date**	5/27/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s) (Information request already communicated to the sponsor)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain: We recommend inspecting bioanalytical studies supporting BE studies because of the pivotal nature of two BE studies.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	1	1288.8 (*exploratory study*): • FDC (lina 5/met XR 1000) vs. lina 5+ 2xmet XR 500 under fasting or fed conditions • 2 x FDC (lina 2.5/met XR 750) vs. lina 5 + 3 x met XR 500
☑ Bioequivalence	3	• 1288.9: FDC (lina 5/ met XR 1000) vs. lina 5 + 2x met XR 500 under fasting or fed conditions • 1288.11: 2 x FDC (lina 2.5/met XR 1000) vs. lina 5 + 4x met XR 500 under fasting or fed conditions • 1288.10 : 2 x FDC (lina 5/ met XR 750) vs. lina 5 + 3x met XR 500 under fasting or fed conditions (*exploratory study*)
☑ Food Effect		Refer the BE studies
☐ Other		
Human Pharmacokinetics		
Healthy Subjects ☑ Single Dose		
Healthy Subjects ☐ Multiple Dose		
Patients ☐ Single Dose		
Patients ☐ Multiple Dose		
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		

☐ Exposure-Safety					
Total Number of Studies	**In Vitro**		**In Vivo**	4	
Total Number of Studies to be Reviewed				4	

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	Note: the application is based on BE studies.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Note: the application is based on BE studies.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	Note: this is a 505(b)(1).
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	Note: the application is based on BE studies.
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	Note: PK data only
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including	☑Yes ☐No ☐N/A	

study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☑No ☐N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo

The sponsor conducted two pivotal BE studies (1288.9 and 1288.11) to support the fixed-dose combination (FDC) of linagliptin and metformin HCl XR.

The sponsor referred to linagliptin NDA (NDA 201280, Tradjenta, AP on 5/2/2011), metformin XR (NDA 21748, Glumetza, AP on 6/3/2005), and FDC of linagliptin and metformin HCl IR (NDA 201281, Jentadueto, AP on 1/30/2012), and indicates this submission is 505(b)(1) with the full right of reference for metformin XR.

The sponsor proposed to market only strengths of 2.5/1000 and 5/1000 based on business decisions. Reference NDAs have strengths as follows (mg/mg):

- Tradjenta – 5 (RLD)
- Glumetza – 500, 1000 (RLD)
- Jentadueto – 2.5/500, 2.5/850, 2.5/1000 (RLD)

Due to the pivotal nature of BE studies, the inspection for the bioanalytical and clinical studies was requested to OSIS through DMEP.

The following information request has been sent out to the sponsor:

Submit the subject level electronic data for Study 1288.10 including at minimum dosing (i.e., period, sequence, treatment/formulation, meal condition), demographic and pharmacokinetic data, preferably as SAS transport (*.xpt) files.

Provide final bioequivalence analysis ready data sets (i.e. Subject ID, Period, Sequence, Treatment/Formulation, Meal Condition, PK parameters such as AUC and Cmax in a single dataset) for all studies (i.e., 1288.8, 1288.9, 1288.10 and 1288.11) as SAS transport (*.xpt) files.

The sponsor's summary indicates that both pivotal study results met the BE criteria as shown below.

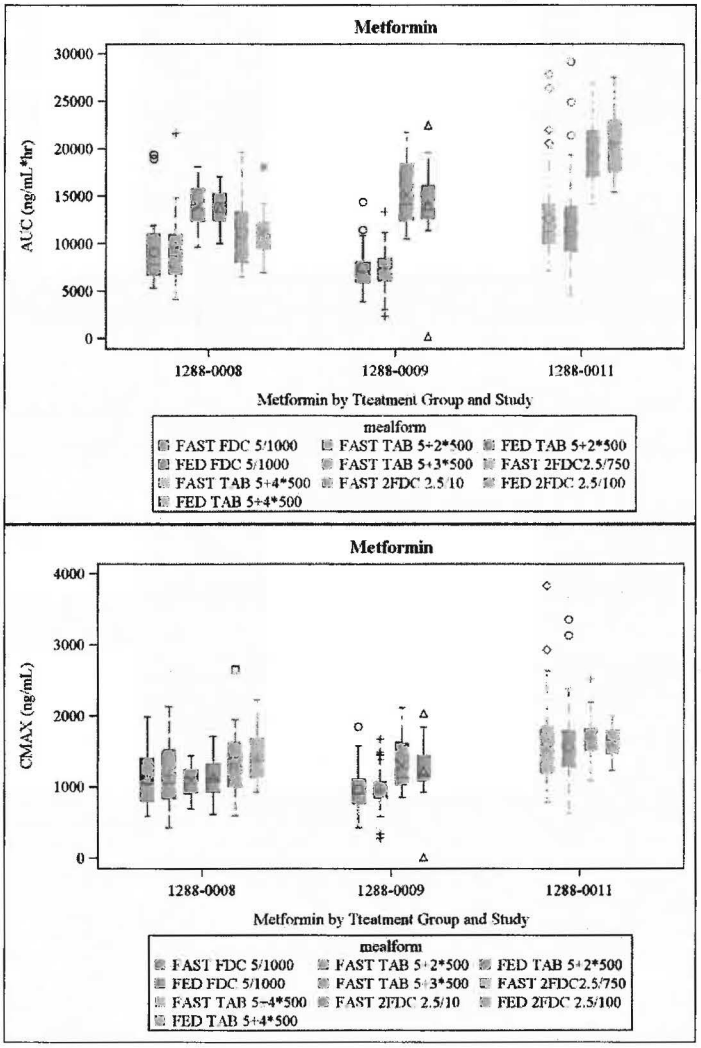
Statistical evaluations for bioequivalence in **Study 1288.9** (dose level investigated: 5 mg/1000 mg)

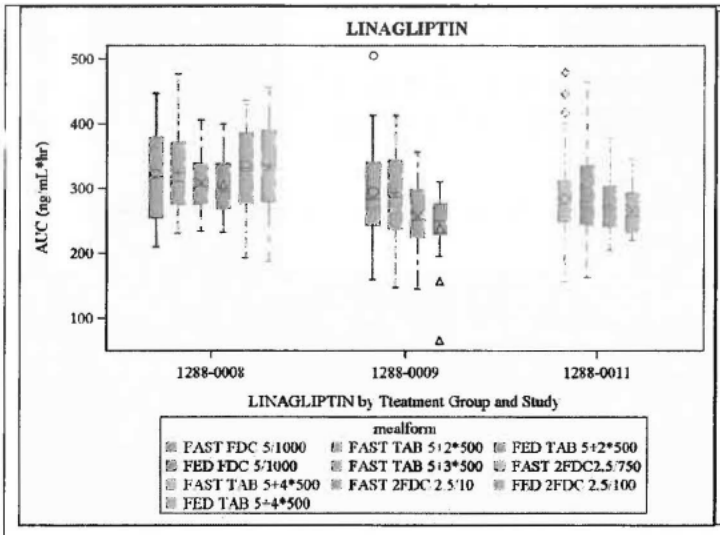
	Part 1 (fasted conditions)		**Part 2 (fed conditions)**	
	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV
Linagliptin				
AUC_{0-72}	100.4 (96.6, 104.3)%	11.8	94.7 (88.7, 101.1)%	9.2
C_{max}	108.1 (99.0, 118.0)%	27.1	98.2 (94.1, 102.6)%	6.1
Metformin				
AUC_{0-tz}	100.0 (93.0, 107.5)%	22.2	97.0 (92.2, 101.9)%	7.1
C_{max}	99.8 (92.5, 107.6)%	23.4	99.0 (95.0, 103.2)%	5.9

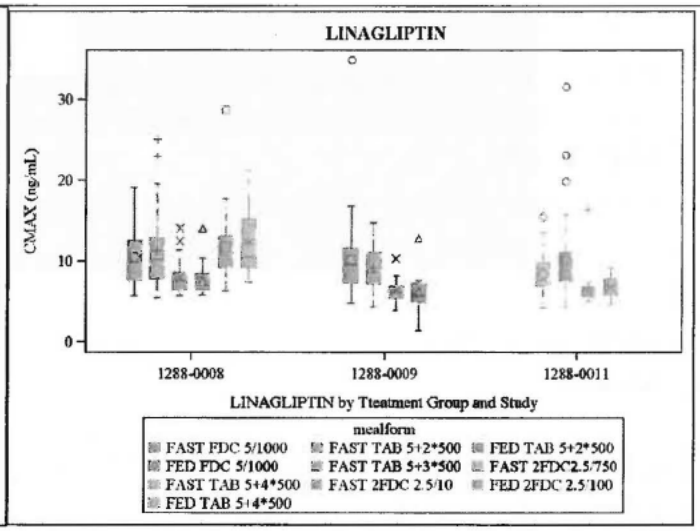
Statistical evaluations for bioequivalence in **Study 1288.11** (dose level investigated: 5 mg/2000 mg)

	Part 1 (fasted conditions)		Part 2 (fed conditions)	
	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV
Linagliptin				
AUC_{0-72}	103.7 (100.7, 106.7)%	9.1	101.6 (93.7, 110.2)%	12.7
C_{max}	114.6 (107.7, 121.9)%	19.6	98.3 (86.5, 111.6)%	20.1
Metformin				
AUC_{0-tz}	96.5 (91.2, 102.0)%	17.6	97.8 (90.5, 105.6)%	11.7
C_{max}	98.0 (92.0, 104.3)%	19.9	105.9 (96.7, 115.9)%	13.8

In general, there was apparent comparability in Cmax and AUC between test (FDC) and reference (co-administration) as shown in the following box plots:







Key Clinical Pharmacology Review Questions are as follows:

1. Are the systemic exposure of linagliptin and metformin from the to-be-marketed FDC formulation bioequivalent to that observed from co-administration of individual linagliptin and metformin XR components?
2. What is the effect of food on the bioavailability of linagliptin and metformin components from the FDC formulation?
3. Are the analytical methods appropriately validated and do they support the claims from the clinical pharmacology studies?

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/s/

SANG M CHUNG
10/02/2015

MANOJ KHURANA
10/02/2015