CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201281Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	201281
Submission Date(s):	01/19/2011
Brand Name:	Trade®
Generic Name:	Linagliptin and Metformin Hydrochloride in combination
Clinical Pharmacology Reviewer:	Manoj Khurana, Ph.D.
Clinical Pharmacology Team Leader:	Jayabharathi Vaidyanathan, Ph.D. (Acting)
OCP Division:	Clinical Pharmacology -2
OND division:	Metabolism and Endocrinology Products
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Type; Code:	NDA 505(b)(2); Standard
Formulation; Strength(s):	Film-coated, Immediate-Release, (b) (4) fixed-dose combination tablets; 2.5 mg Linagliptin / 500 mg Metformin HCl, 2.5 mg Linagliptin / 850 mg Metformin HCl, and 2.5 mg Linagliptin / 1000 mg Metformin HCl
Proposed Indication:	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with linagliptin and metformin is appropriate

List of Figures and Tables

Note to readers:

- At the time of compilation of this review the trade name is not finalized. Therefore it is referred to as "Trade®" throughout the review
- Throughout this review, treatments are designated as follows:
  - "L+M," "lina+met," and "linagliptin+metformin": used interchangeably to represent any dosage of the free combination therapy with linagliptin and metformin
  - "L/M," "lina/met," and "linagliptin/metformin": only used for the single-tablet (fixed-dose) combination formulation

1 Executive Summary

Boehringer Ingelheim Pharmaceuticals, Inc. (hereafter BI/the sponsor) is seeking an approval of Trade®;Linagliptin (L) + Metformin hydrochloride (M) (hereafter L/M) film-coated fixed-dose combination (FDC) tablets for the treatment of type 2 diabetes mellitus (T2DM). The proposed indication for L/M is "*an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with linagliptin and metformin is appropriate*". The active pharmaceutical ingredients in L/M drug product are linagliptin, a dipeptidyl peptidase (DPP4) inhibitor, and metformin HCl, a widely prescribed oral antidiabetic.

The proposed FDC will be available as three dosage strength immediate-release tablets:

- 2.5 mg Linagliptin / 500 mg Metformin HCl,
- 2.5 mg Linagliptin / 850 mg Metformin HCl, and
- 2.5 mg Linagliptin / 1000 mg Metformin HCl

The proposed recommended daily dose of Trade® is one tablet taken twice daily (BID).

Since both active ingredients are approved in the US for use in T2DM, this application is submitted by the sponsor as a 505(b)(2) NDA. The sponsor has referenced pertinent information from approved US prescribing information for Tradjenta® (linagliptin; NDA 201280) and Glucophage® (metformin hydrochloride; NDA 20-357).

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA 201281 for Trade®. The clinical pharmacology information submitted under this NDA is acceptable and supports a recommendation of approval of Trade®.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

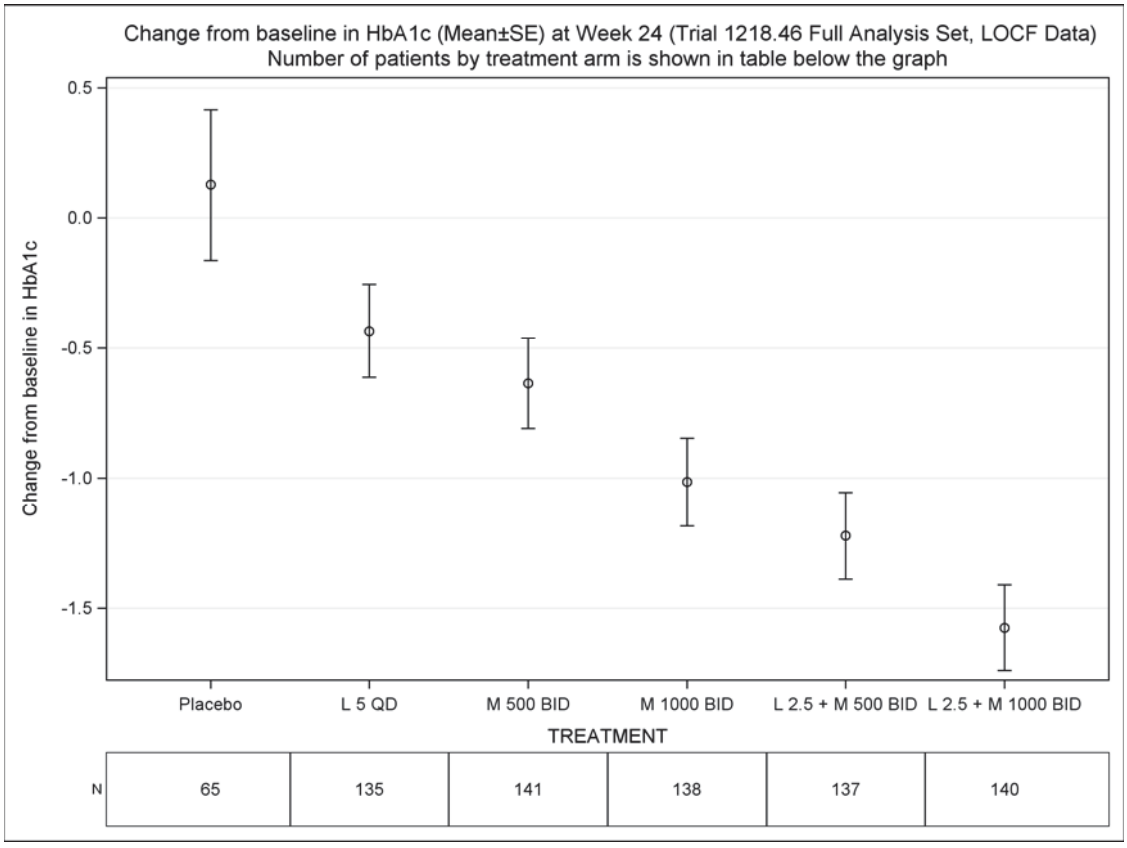
The efficacy and safety of the concomitant use of linagliptin and metformin has been reviewed in the NDA 201280 for Tradjenta® (Linagliptin). The Trade® clinical development program is composed of 13 clinical studies: 6 Phase I studies (one of these, 1218.4, was conducted as part of the development of linagliptin as monotherapy), one Phase 2 study (also part of the monotherapy

development program), and 6 Phase 3 studies, 2 of which were long-term extensions. At the time of this NDA submission, 10 of these studies were completed; for the 3 ongoing studies (1218.20, 1218.40, and 1218.52) results of the planned interim analyses were included. Study 1218.57, which was conducted to show bioequivalence between the European sourced Glucophage® (used in Pivotal Phase 3 Study 1218.46) and US Glucophage® reference products, was also conducted as part of the development of the fixed-dose combination for linagliptin and metformin. Clinical Pharmacology review of the information submitted by the sponsor, in support of their application, revealed the following important findings:

Dose -Response for HbA1c (Efficacy)/safety:

- Dose-response relationship demonstrated additional reduction in HbA1c with co-administration of 2.5 mg linagliptin and metformin 500 mg BID or 1000 mg BID over linagliptin 5 mg QD, metformin 500 mg and metformin 1000 mg BID monotherapy in a 24-week therapy (Trial 1218.46) (Figure. 1).
- The linagliptin 2.5 mg/metformin 1000 mg provided numerically higher reduction in HbA1c over the linagliptin 2.5 mg/metformin 500 mg BID dose in a 24-week therapy (Trial 1218.46)
- 5 mg dose was more likely to achieve >80% inhibition of DPP-4 at steady state compared to 2.5 mg dose.
- Overall, the percentages of patients with adverse events (AEs) were comparable between treatment groups, ranging from 49.0% in the Lina 2.5 + Met 500 group to 56.6% in the Lina 2.5 + Met 1000 group.

Figure 1 Combination treatment provides numerically higher HbA1c reduction versus the linagliptin and metformin given as monotherapy in the 24-week Phase 3 confirmatory trial (1218.46)



General ADME:

Linagliptin: The linagliptin pharmacokinetic profile from Trade® was similar to that observed with the administration of linagliptin alone.

Metformin: The metformin pharmacokinetic profile from Trade® was similar to that observed with the administration of metformin alone.

Intrinsic Factors (Body weight, Age, BMI, Gender, Race, Genetics etc.) Affecting Exposure:

None of the covariates are known to affect either linagliptin or metformin pharmacokinetics and no dose adjustments are proposed based on these in the individual product labels. Therefore, no dose adjustments are warranted for Trade® based on any of these covariates.

Specific Populations

Elderly patients: In the elderly, Trade® should be carefully titrated to establish the minimum dose for adequate glycemic effect and should be based on the age-appropriate upper limit of creatinine clearance as aging can be associated with reduced renal function. Before initiation of therapy with Trade® and at least annually thereafter, renal function should be assessed.

Renal Impairment: Effect of renal impairment on linagliptin and metformin PK from Trade® was not specifically evaluated. While no dose adjustment is recommended for linagliptin in patients with renal impairment, risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, in accordance with the current labeling recommendations for metformin, patients with renal impairment (e.g., serum creatinine >1.5 mg/dL [males] or >1.4 mg/dL [females], or abnormal creatinine clearance) should not receive Trade®. In patients in whom development of renal dysfunction is anticipated, including elderly patients, renal function should be assessed more frequently and Trade® discontinued if evidence of renal impairment is present.

Hepatic Impairment: Effect of hepatic impairment was not evaluated specifically for Trade®. While no dose adjustment of linagliptin is recommended in patients with hepatic impairment, impaired hepatic function has been associated with cases of lactic acidosis with metformin therapy as impaired hepatic function may significantly limit the ability to clear lactate. Therefore, Trade® use should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

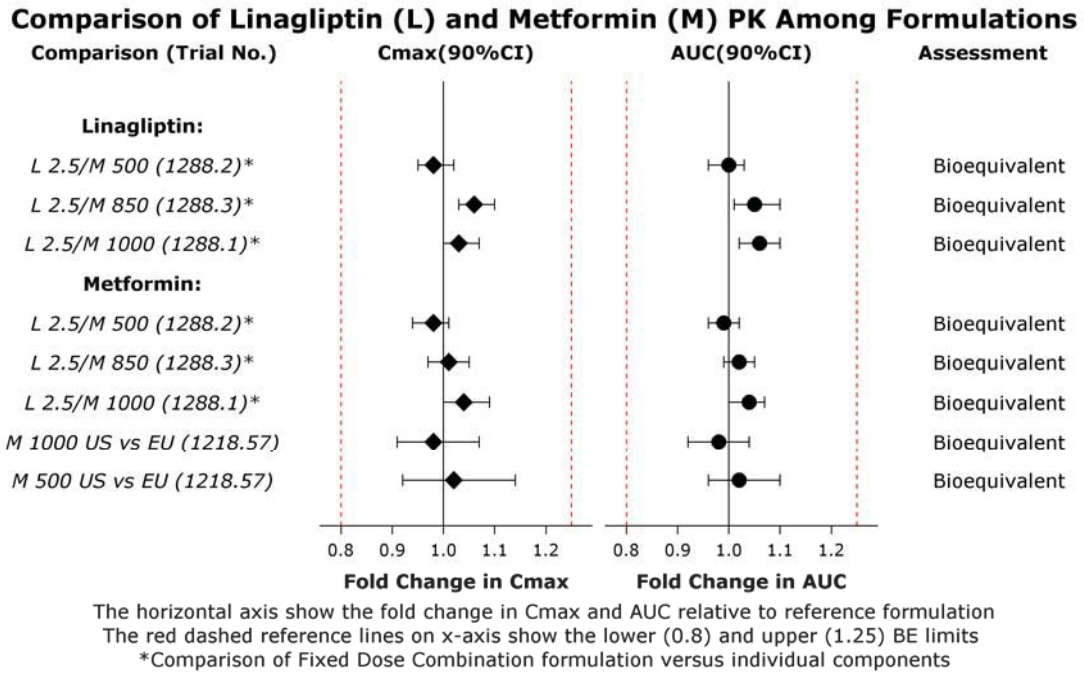
Extrinsic Factors:

Food Effect: Food lowered the peak exposure of metformin from the Trade® formulation by 18% and from a clinical pharmacology perspective Trade® could be taken with or without food. However, considering that metformin is administered with food to improve the gastrointestinal tolerability, the Trade® is indicated to be administered with food.

PK Comparison of Intended Commercial vs. Phase 3 Formulations:
Bioequivalence was demonstrated between intended commercial FDC formulation and co-administration of Phase 3 individual tablet formulations for Linagliptin 2.5/Metformin 500 mg and Linagliptin 2.5/Metformin 1000 mg FDC. Bioequivalence was demonstrated between intended commercial FDC formulation and co-administration of individual tablet formulations for Linagliptin 2.5/Metformin 850 mg, and also between the EU sourced Glucophage® formulation

(used in the pivotal Phase 3 trial and all BE studies) and the US approved Glucophage® formulation.

Figure 2 Trade® fixed-dose combination formulation is bioequivalent to co-administration of individual components for linagliptin and metformin.



The horizontal axis show the fold change in Cmax and AUC relative to reference formulation
The red dashed reference lines on x-axis show the lower (0.8) and upper (1.25) BE limits
*Comparison of Fixed Dose Combination formulation versus individual components

Bioanalytical Methodology:

For the clinical pharmacology assessments, linagliptin and metformin were quantitated in plasma using validated HPLC-MS/MS assay methods. The assay methods were validated for analyzing these 2 analytes in plasma samples in terms of range, accuracy, precision and sensitivity. The changes to the analytical sites or procedures were adequately supported by partial/cross validation of methods whenever necessary.

2 Question Based Review

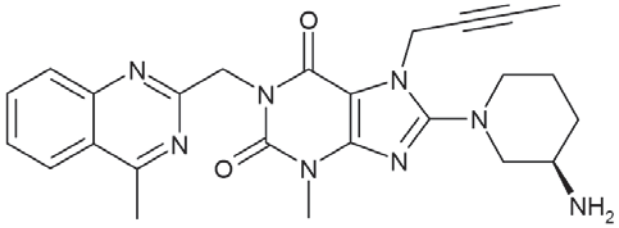
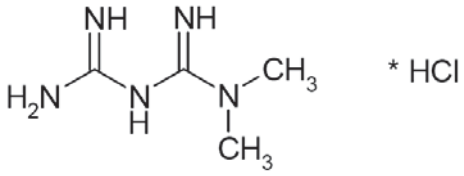
2.1 General Attributes

BI is seeking the approval of combination product Trade® (Linagliptin and Metformin HCl FDC) Immediate-Release Tablets, for the treatment of type 2 diabetes mellitus (T2DM). Linagliptin (Figure 3a) is an approved DPP-4 inhibitor and metformin (Figure 3b) is an approved biguanide, both are indicated for the treatment of type 2 diabetes mellitus. Trade® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate.

Since both active ingredients are approved in the US for T2DM, sponsor submitted a 505(b)(2) NDA, and referenced pertinent information from approved US prescribing information for Tradjenta® (linagliptin; NDA 201280 approved 05/02/2011) and Glucophage® (metformin hydrochloride; NDA 20-357).

The chemical structures of linagliptin and metformin are illustrated in Figure 3 below:

Figure 3 Chemical Structures of Linagliptin and Metformin.

(a) Linagliptin	(b) Metformin hydrochloride
	

Linagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme which rapidly degrades incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Linagliptin binds in a reversible manner selectively to DPP-4 and exhibits a >10,000-fold selectivity versus DPP-8 or DPP-9 activity.

Metformin is a biguanide that works by increasing insulin sensitivity and decreasing hepatic glucose production.

Sponsor's intent of combining linagliptin with metformin hydrochloride is based on convenience for patients. The combination would allow decreasing the number of tablets to be taken by the patient and improve patient compliance with medication.

The sponsor has supported the Trade® application with clinical pharmacology studies, which compare intended commercial drug product formulations with the Phase 3 individual formulations, evaluate food effect, and DDI between linagliptin and metformin.

2.1.1 What are the proposed dosage regimens for Trade®?

The proposed Trade® tablet is a film-coated, immediate-release, (b) (4) tablet containing the two drugs and excipients. Trade® is available as three dosage strength tablets:

- 2.5 mg Linagliptin / 500 mg Metformin HCL,
- 2.5 mg Linagliptin / 850 mg Metformin HCL, and
- 2.5 mg Linagliptin / 1000 mg Metformin HCL.

Treatment with the linagliptin/metformin (L/M) FDC is recommended for:

- Adults with T2DM when treatment with both linagliptin and metformin is appropriate including-
    - patients who have been previously treated with the free combination of both components,
    - patients treated with either metformin or linagliptin monotherapy, (b) (4) (b) (4)

Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health-care provider. In accordance with the recommended dosing schedule for metformin, metformin therapy should be gradually increased from lower starting doses (such as 500 mg BID) to minimize gastrointestinal symptoms. The maximum recommended daily dose of the L/M combination is 5 mg linagliptin plus 2000 mg metformin (given as 2.5/1000 mg BID).

(b) (4) patients may begin with the Trade® 2.5/500 mg dose. For patients whose HbA1c is poorly controlled (i.e., ≥11.0%), treatment with a Trade® dose of 2.5/1000 mg BID could be recommended, with initial titration of the metformin component from 500 mg BID after 2 weeks.
Compared to metformin 1000 mg BID monotherapy, the L+M 2.5/500 mg BID dose presents comparable efficacy and a safety profile that is relatively free of the GI events normally associated with the 1000 mg BID dose of metformin. Therefore, the Trade® 2.5/500 mg BID dose represents an alternative for patients who cannot tolerate the GI side effects associated with the higher dose of metformin.

The two tablet strengths of Trade® L/M 2.5/500 mg or L/M 2.5/1000 mg tablet are designed to enable the titration regimen for metformin component after treatment initiation. The availability of L/M 2.5 /850 mg tablet would allow for dosing of subject who cannot tolerate 1000 mg BID metformin and help in titration of Trade®.

2.1.2 What is the composition of the intended commercial Trade® formulation?

The details on the tablet composition and manufacturing should be referred to the CMC review. In brief, the proposed commercial presentations of Trade® are film-coated, immediate-release (b) (4) tablets. The three presentations of the intended commercial drug product (i.e. L/M 2.5/500 mg, 2.5/850 mg and 2.5/1000 mg) differ in the amount of metformin (b) (4) (b) (4) (b) (4) (b) (4) The compositions of L/M tablets are listed in Table 1 below.

Table 1 Quantitative Composition of the Trade® Tablets

		linagliptin / metformin hydrochloride		
		2.5 mg / 500 mg	2.5 mg / 850 mg	2.5 mg / 1000 mg
Ingredient	**Function**	**[mg/ tablet]**	**[mg/ tablet]**	**[mg/ tablet]**
Linagliptin	Active ingredient	2.500	2.500	2.500
Metformin hydrochloride	Active ingredient	500.000	850.000	1000.000
Arginine	(b) (4)			
Corn starch				
Copovidone				
Colloidal silicon dioxide				
Magnesium stearate				
(b) (4)				
Titanium dioxide				
Yellow ferric oxide				
Red ferric oxide				
Propylene glycol				
Hypromellose (b) (4)				
Talc				
(b) (4)				
	Total weight (film coated tablet)	**602.0**	**1016.0**	**1198.0**

(b) (4)

The approved dose of linagliptin is 5 mg once a day (NDA 201280). Metformin hydrochloride is approved in the US in dose strengths of 500 mg, 850 mg and 1000 mg for a BID use. The development of the combination product was intended to match this metformin regimen, and thus, the therapeutic dose of linagliptin of 5 mg once a day was split into two doses of 2.5 mg each.

The supplies for the three bioequivalence studies (1288.1 - 1288.3) were manufactured (b) (4) (b) (4) (See Table 2).

Table 2 Approximate yields for (b) (4) batch size

Dosage strength	**Approximate yield** (b) (4) **number of film coated tablets)**
2.5 mg/500 mg	(b) (4)
2.5 mg/850 mg	
2.5 mg/1000 mg	

2.2 General Clinical Pharmacology

2.2.1 What are the known genral clinical pharmacology characteristics of linagliptin and metformin after oral administration, in the context of current application?

The detailed clinical pharmacology information can be found in the prescribing information for the approved linagliptin and metformin products. The key aspects are mentioned below:
Linagliptin:

- Follows non-linear PK for doses ranging from 1 mg to 600 mg. Increases in exposures were less than dose proportional for the dose range of 1 mg to 10 mg, more than dose proportional for the dose range of 25 mg to 100 mg, and almost dose proportional for the dose range of 100 mg to 600 mg. The non-linearity in dose range of 1 to 10 mg and long half-life of linagliptin (i.e., >100 hours) may partially be explained by concentration dependent binding to dipeptidyl peptidase-4 (DPP-4). At concentrations of 1 nM, almost 99% of drug remains bound to DPP-4, which reduced to 70-80% at concentrations of about 100 nM.
- The accumulation half-life of linagliptin ranges from 8-12 hours.
- The majority of drug is eliminated unchanged in feces (~85%) and a minor proportion appears in urine (~4.5%). Metabolism is a minor pathway of elimination for linagliptin. However, linagliptin appears to undergo enterohepatic re-circulation.
- The predominant metabolite, CD1790 (formed by CYP3A4 isoform), is therapeutically inactive.
- Co-administration with high-fat meal reduced linagliptin rate of absorption (i.e., Cmax) by ~15 to 25% but had no effect on AUC. These changes were not considered clinically relevant.
- The extent of DPP-4 inhibition increased with increases in linagliptin doses from 1 to 10 mg. Average steady-state DPP-4 inhibitions at 24 hours after the last dose were 62.5%, 76.9%, 85%, and 89.4% for 1 mg, 2.5 mg, 5 mg, and 10 mg dose groups, respectively.

Metformin (Glucophage®):

- Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
- The absolute bioavailability of a Glucophage® 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Glucophage® 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.
- Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.
- The apparent volume of distribution (V/F) of metformin following single oral doses of Glucophage® 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Glucophage®, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1000 ng/mL.

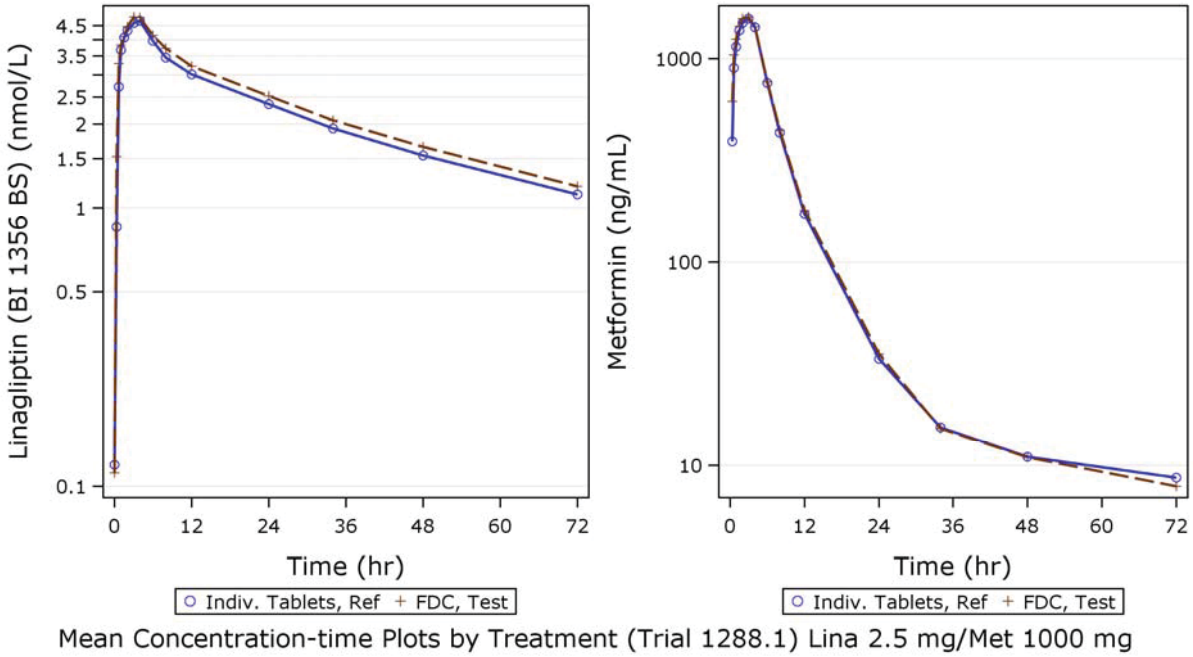
- Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.[1]

2.2.2 What are the PK characteristics of linagliptin and metformin from Trade® formulation after oral administration and how do they compare to the Phase 3 individual tablet formulations?

A representative mean plasma concentration time profiles of linagliptin and metformin from one of the BE studies (1288.1), comparing Trade® formulation (single oral dose of Lina 2.5/Met 1000 mg FDC) versus single co-administration of Lina 2.5 mg and Met 1000 mg IR (Glucophage®) formulations, are presented in Figure 4 below.

On average, the systemic exposures of both linagliptin and metformin from Lina 2.5/Met 1000 mg FDC were comparable to that observed from co-administration of individual Lina 2.5 mg and Met 1000 mg IR formulations used in Phase 3 trial.

Figure 4 Mean plasma concentration time profile of linagliptin and metformin after single oral dose of Lina 2.5 /Met 1000 mg FDC tablet (red dashed line) versus single co-administration of Lina 2.5 mg and Met 1000 mg IR formulations (blue solid line) under fasted state



[1] Glucophage® prescribing information, NDA 20357.

The summary of pharmacokinetic parameters for linagliptin and metformin from the BE study (1288.1), comparing Trade® formulation (single oral dose of Lina 2.5/Met 1000 mg FDC) versus single co-administration of Lina 2.5 mg and Met 1000 mg IR (Glucophage®) formulations, are presented below in Table 3 and 4, respectively. The pharmacokinetics of linagliptin and metformin from FDC formulation was comparable to that observed with co-administration of individual components.

Table 3 Summary of key linagliptin pharmacokinetic parameters after single oral dose of Lina 2.5 /Met 1000 mg FDC tablet versus single co-administration of Lina 2.5 mg and Met 1000 mg IR formulations

Treatment	N	Parameter	N	Mean	Std Dev	Median
FDC	96	Cmax	96	5.20	1.25	5.15
		Tmax	96	2.98	1.10	3.00
		T1/2	96	42.66	5.71	42.44
		AUC0-t	96	163.36	45.92	160.73
		AUC0-inf	96	238.12	72.84	222.20
Individual Formulations	95	Cmax	95	5.04	1.19	5.04
		Tmax	95	3.17	1.15	3.00
		T1/2	95	42.98	6.38	42.59
		AUC0-t	95	153.14	39.19	150.74
		AUC0-inf	95	223.61	60.98	211.00

Table 4 Summary of key metformin pharmacokinetic parameters after single oral dose of Lina 2.5 /Met 1000 mg FDC tablet versus single dose of Lina 2.5 mg and Met 1000 mg IR formulations

Treatment	N	Parameter	N	Mean	Std Dev	Median
FDC	96	Cmax	96	1742.55	462.24	1735.00
		Tmax	96	2.53	0.85	2.50
		T1/2	96	9.31	4.17	7.71
		AUC0-t	96	11261.86	2927.02	11041.36
		AUC0-inf	96	11393.35	2904.13	11197.73
Individual Formulations	95	Cmax	95	1675.67	485.72	1570.00
		Tmax	95	2.74	0.83	3.00
		T1/2	95	9.21	4.09	8.30
		AUC0-t	95	10838.50	2881.78	10402.47
		AUC0-inf	95	10965.11	2871.46	10499.40

The statistical comparison of PK parameters is described later under question 2.5.1.

2.2.3 What are the pharmacokinetic/pharmacodynamic characteristics of linagliptin after oral administration of the 2.5 mg BID and 5 mg QD dose?

Currently approved dose for linagliptin is 5 mg QD. However, to match the schedule of BID dosing regimen of metformin, the linagliptin dose was split into two doses each of 2.5 mg. Sponsor did not submit linagliptin 2.5 mg BID versus 5 mg QD efficacy comparison. However, sponsor claims that 2.5 mg BID and 5 mg QD provide similar exposure of linagliptin and extent

of DPP4 inhibition. The linagliptin exposure-DPP4 inhibition relationship was evaluated in a multiple dose PKPD study in healthy subjects (n=16). Linagliptin was administered as 2.5 BID or 5 mg QD for 14 days. The samples for PKPD assessment were collected on two consecutive days on Day 14. The DPP4 inhibition corresponding to the linagliptin concentration observed for the two regimens is presented in Figure 5 below. The linagliptin exposure-DPP4 inhibition relationship overlapped between the 2.5 mg BID and 5 mg QD regimen in Phase 1 trial (1218.45) and pivotal phase 3 trial (1218.46) (Figure 5).

Figure 5 PKPD Relationship of linagliptin for DPP4 inhibition

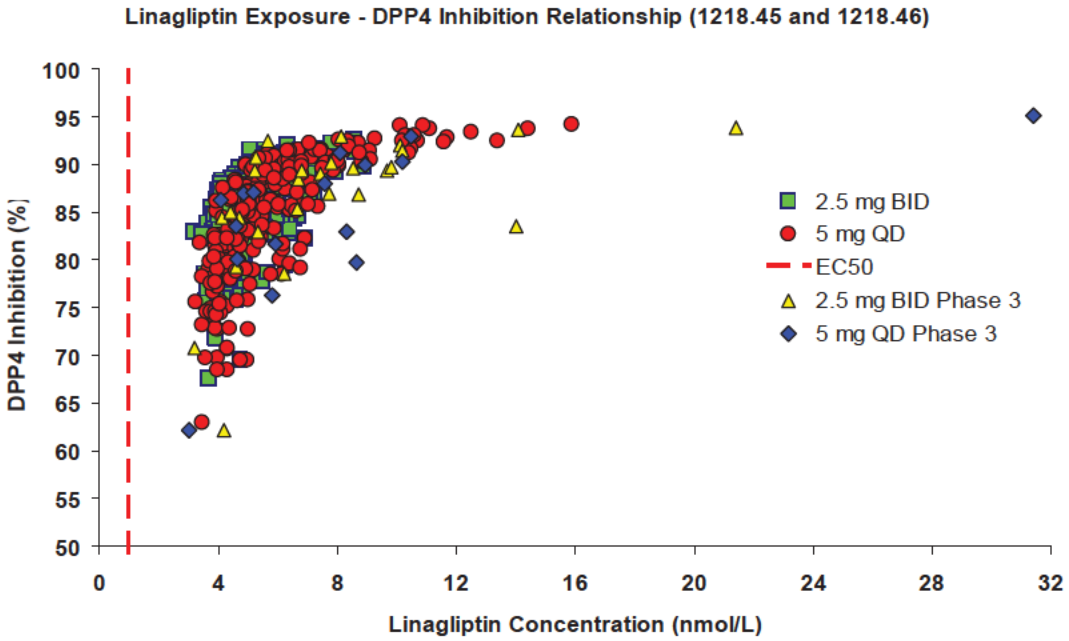


Table 5 Summary of linagliptin PK and DPP4 inhibition observed with 2.5 mg BID and 5 mg QD regimens

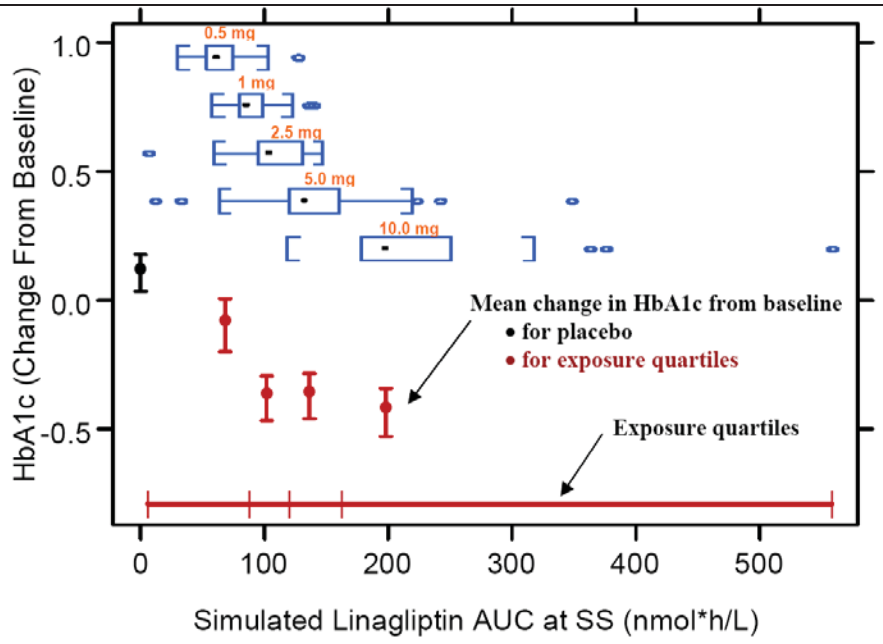
	Linagliptin Concentration (nmol/L)		DPP4 Inhibition (%)	
	2.5 mg BID	**5 mg QD**	**2.5 mg BID**	**5 mg QD**
Mean	5.25	5.90	85.46	84.88
Standard Deviation	0.98	2.02	4.08	6.27
Median	5.09	5.37	86.19	86.13
Minimum	3.16	3.22	67.54	63.01
Maximum	8.91	15.9	92.55	94.13

The results showed that linagliptin daily dosing for 14 days resulted in average inhibition in excess of 80% for both the 2.5 mg BID and 5 mg QD dose regimens (Table 5). However, the relevance of 80% lower cut-off used by the sponsor for the DPP4 inhibition to efficacy and safety aspect of linagliptin, and the FDC thereof, is not well understood. Additionally, the relationship between the extent/duration of DPP4 inhibition and HbA1c reduction is not well defined. On other hand, the linagliptin exposure-response was evaluated during the review of original NDA (Fig. 6a), which revealed that change in HbA1c from baseline (ΔHbA1c) increased with

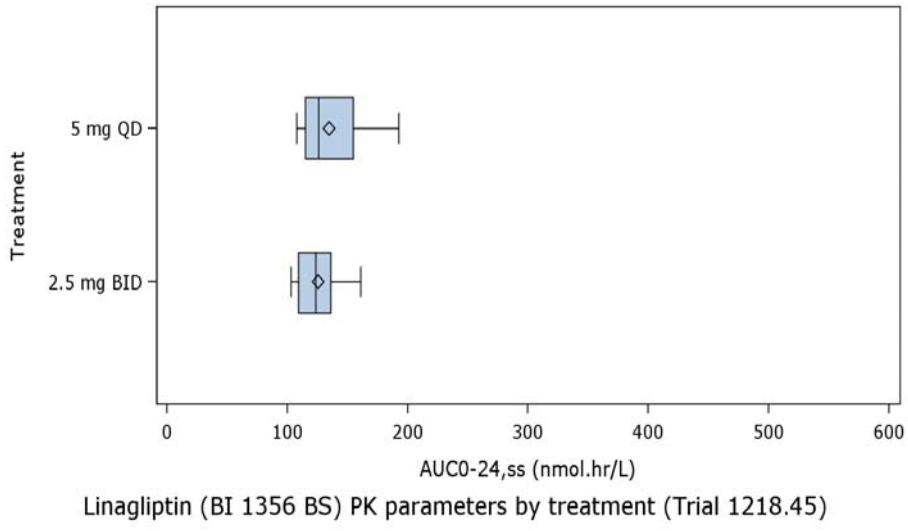
increasing exposure and reached a plateau at exposures greater than approximately 100 nM*h (2). The PKPD study shows that both 2.5 mg BID and 5 mg QD result in steady-state AUC0-24h well above this value (Fig. 6b), and thus can be reasonably expected to result in similar HbA1c response.

Figure 6 **Linagliptin exposure-response for efficacy support the use of 2.5 mg BID under fixed-dose regimen with metformin**

(a)(3)



(b)



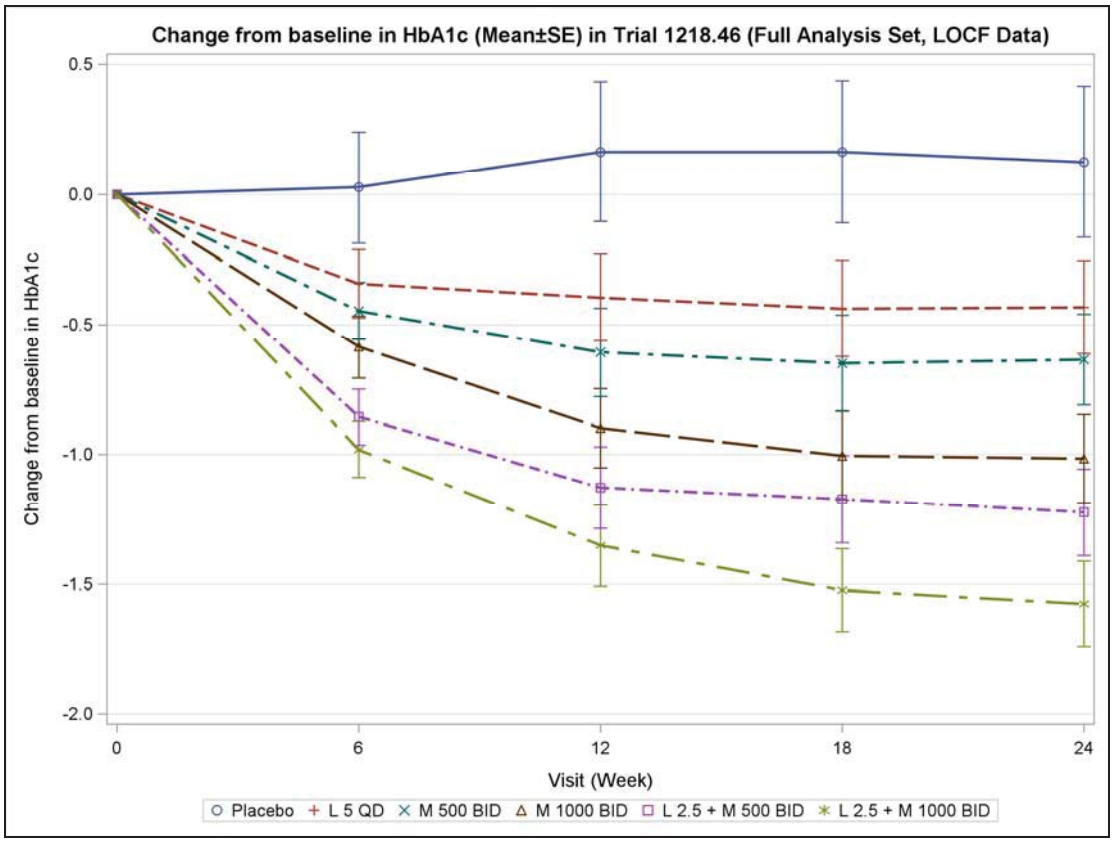
[2] ***Dr. Lokesh Jain's Clinical Pharmacology Review of NDA 201280 in DAARTS dated 03/09/2011***
[3] ***Figure 13: Exposure-Response Relationship Based on Simulated Exposures for Phase 2 trials 1218.5 & 1218.6 from Dr. Lokesh Jain's Clinical Pharmacology Review in DAARTS dated 03/09/2011)***

2.2.4 What are the characteristics of the Trade® exposure-response relationship (dose-response, concentration-response) for HbA1c reduction (efficacy) in T2DM patients?

The efficacy and safety of co-administration of linagliptin with metformin has been reviewed in the original NDA, where linagliptin 5 mg use as an add-on therapy to metformin was evaluated in the T2DM patient population. A single, well-controlled Phase 3 Trial 1218.46 was conducted to support the linagliptin / metformin FDC tablets. In this trial single entity tablets linagliptin (2.5 mg and 5 mg tablets) and metformin (Glucophage® 500 and 1000 mg – EU commercial tablets) and the corresponding placebo formulations were used. Therein the efficacy/safety of therapeutic mechanisms was evaluated for the lower dose strength of L 2.5 + M 500 mg and the higher dose strength of L 2.5 + M 1000 mg.

The change from baseline in HbA1c versus time profile in pivotal Phase 3 trial 1218.46 is presented by treatment in Fig. 7 below. Trial 1218.46 tested two doses of the combination therapy (L 2.5+M 500 mg and L 2.5+M 1000 mg both BID) and the monotherapy with placebo, M 500 mg, M 1000 mg as BID and L 5 mg QD. The trial results show that the maximal mean reduction in HbA1c from baseline is achieved after week 20 in both low (L 2.5+M 500 mg) and high dose (L 2.5+M 1000 mg) treatment arms. These two treatment arms differed in the total daily metformin dose; 1000 mg versus 2000 mg, while receiving same total daily dose of linagliptin 5 mg.

Figure 7 Time course of change in HbA1c from baseline in the 24-week Phase 3 confirmatory trial (1218.46)

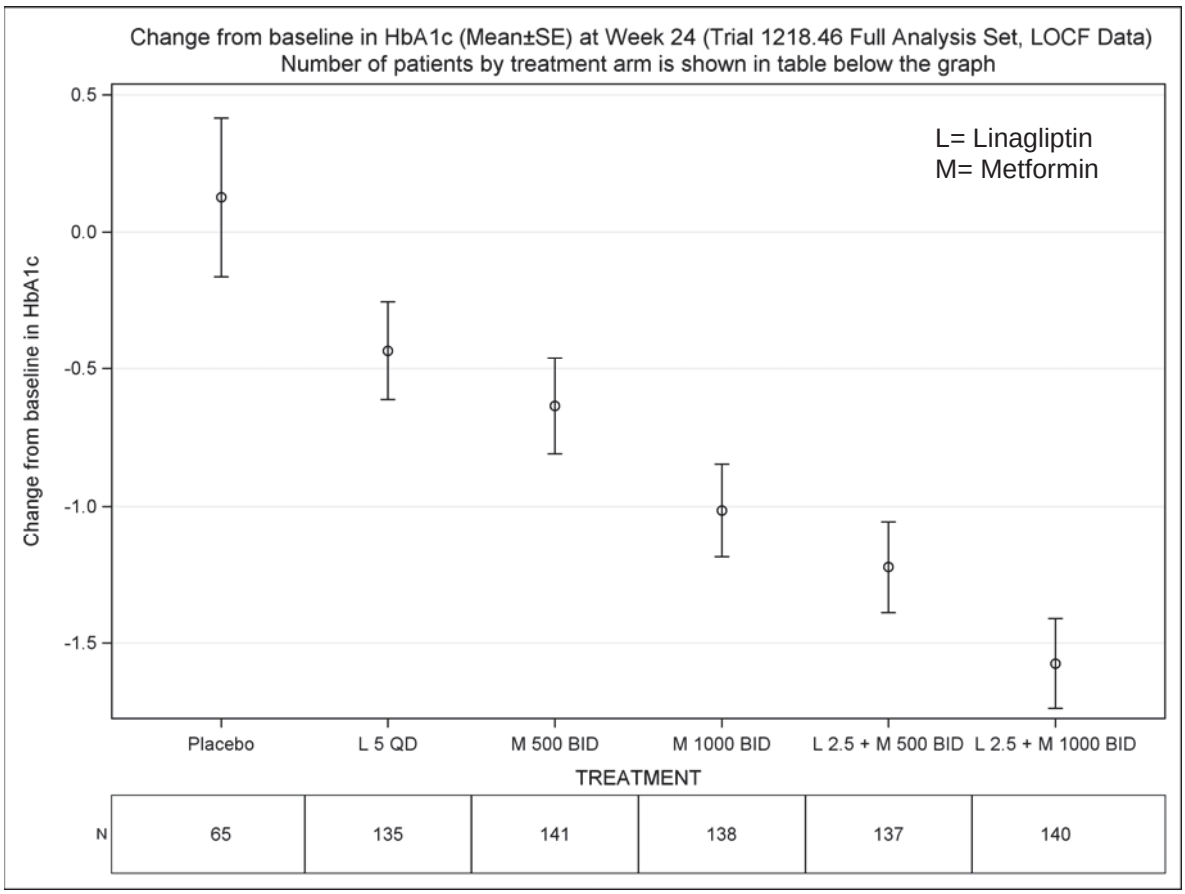


The dose-change in HbA1c relationship at week 24 from this trial shows that Trade® treatment (combination use) is associated with a dose dependent reduction in HbA1c from baseline among Lina 2.5 mg + Met 500 mg and Lina 2.5 mg + Met 1000 mg treatment arms, which is numerically

greater in comparison to the reduction observed with Lina 5 mg QD, Met 500 BID and Met 1000 mg BID alone arms (Figure 8).

These results adequately support the proposed dosing regimen for the Trade® in T2DM population.

Figure 8 Combination of Linagliptin and Metformin results in additive reduction in HbA1c versus monotherapy based on Mean(±SE) change from baseline in HbA1c at week 24 (Phase 3 trial 1218.46)



2.2.5 What are the characteristics of the exposure-response relationship (dose-response, concentration-response) for safety with regards to hypoglycemic adverse reactions in T2DM patients when linagliptin and metformin are co-administered?

The safety results for the linagliptin 2.5 mg BID was evaluated in the factorial design trial. Overall, the percentages of patients with AEs were comparable between treatment groups, ranging from 49.0% in the Lina 2.5 + Met 500 group to 56.6% in the Lina 2.5 + Met 1000 group. Patients with adverse events were most frequently reported in the system organ classes (SOCs) gastrointestinal disorders (ranging from 9.7% to 19.6%), infections and infestations (ranging from 16.3% to 23.1%), metabolism and nutrition disorders (ranging from 4.9% to 16.7%), and nervous system disorders (ranging from 3.4% to 13.9%).Within gastrointestinal disorders, the percentage of patients with AEs was lowest in the met 500 group (9.7%) and highest in the Lina 2.5 + Met 1000 group (19.6%) compared to the remaining treatment groups, which had comparable

percentages of patients with gastrointestinal AEs (ranging from 12.0% to 15.6%). On the preferred term level, diarrhea was reported most frequently in all treatment groups, with the highest frequency reported in the Lina 2.5 + Met 1000 group (7.7%).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effects of various intrinsic factors (e.g., hepatic, renal, gender, elderly) were provided in the original NDA for each drug. Please see Clinical Pharmacology reviews for NDA 201280 (for Linagliptin, Tradjenta®) and NDA 20-357 (for Glucophage®). Based on the approved label information for the lingagliptin and metformin, no dose adjustments are recommended for any of the intrinsic factors including weight, gender, race, renal or hepatic impairment. However, since renal function could decrease with age, the Trade® is proposed to be used in elderly (age > 65) only after assessing and ensuring that the renal function is normal. Periodic assessment of renal function is recommended annually. This approach is acceptable from a clinical pharmacology perspective.

2.3.2 Does the renal function affect linagliptin and metformin pharmacokinetics from Trade®?

Effect of renal impairment on linagliptin and metformin PK from Trade® was not specifically evaluated. Based on the approved Tradjenta® label, no dose adjustment is recommended for linagliptin in patients with renal impairment. However, based on the approved Glucophage® label, risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, sponsor proposed that patients with renal impairment (e.g., serum creatinine >1.5 mg/dL [males] or >1.4 mg/dL [females], or abnormal creatinine clearance) should not receive Trade®. In the elderly, Trade® should be carefully titrated to establish the minimum dose for adequate glycemic effect and should be based on the age-appropriate upper limit of creatinine clearance as aging can be associated with reduced renal function. Before initiation of therapy with Trade® and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and Trade® discontinued if evidence of renal impairment is present. Sponsor's proposal is acceptable.

2.3.3 Does the hepatic function affect linagliptin and metformin pharmacokinetics from Trade®?

Effect of hepatic impairment was not evaluated specifically for Trade®. Based on the approved Tradjenta® label, no dose adjustment of linagliptin is necessary in patients with hepatic impairment. However, based on the approved Glucophage® label, impaired hepatic function has been associated with cases of lactic acidosis with metformin therapy. As impaired hepatic function may significantly limit the ability to clear lactate, the label recommends that Glucophage® use should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Therefore, the sponsor proposed that Trade® tablets should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Sponsor's proposal is acceptable.

2.3.3 What is the proposed use of Trade® in pediatric subjects?

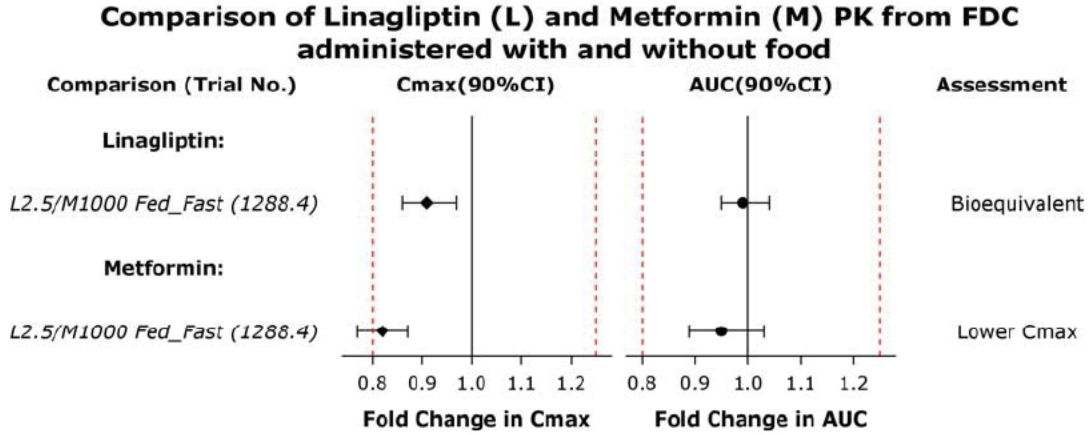
Safety and effectiveness of Trade® in pediatric patients has not been evaluated yet. Sponsor has submitted the pediatric plan (same plan submitted under Tradjenta NDA 201280) and which will be presented to PeRC on October 12, 2011. Sponsor has requested a partial waiver for the pediatric population ≤9 years of age. For age groups 10 to (b) (4) years, sponsor is proposing two clinical trials: (1) A randomized, double-blind, placebo-controlled parallel group dose-finding study of linagliptin (1 mg and 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to (b) (4) years of age, with T2DM and insufficient glycemic control despite treatment with diet and exercise alone, and (b) (4)

2.4 Extrinsic Factors

2.4.1 What is the effect of food on the bioavailability of linagliptin and metformin from Trade®?

Single oral dose food effect study showed that when given with high-fat diet, linagliptin Cmax was slightly decreased by ~10% without any changes in AUC, though the geometric mean ratios and the 90% confidence intervals were within the pre-specified limits of 80-125% under fed versus the fasted condition. Metformin peak and total exposure were also decreased in the presence of high-fat diet by 20% and 15%, respectively. The results of the statistical analysis of linagliptin and metformin PK parameters from this single dose food effect study are summarized in Figure 9 below.

Figure 9 Effect of food on linagliptin and metformin exposure from Trade®



The horizontal axis show the fold change in Cmax and AUC relative to reference formulation
The red dashed reference lines on x-axis show the lower (0.8) and upper (1.25) BE limits

Metformin is recommended to be administered with food to reduce the gastro-intestinal adverse effects. The observed effect of food on linagliptin and metformin PK from the Trade® are in accordance with those reported for the individual components. Therefore, from clinical pharmacology perspective Trade® can be taken with or without food as has been recommended for the individual components.

2.4.2 Drug-Drug Interactions (DDIs)

2.4.2.1 What is the CYP inhibition potential of linagliptin and metformin?

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11. Linagliptin is a P-gp substrate, and inhibits P-gp mediated transport of digoxin with low potency.

For metformin, sponsor investigated the *in vitro* inhibition of cytochrome P450-catalysed test reactions by metformin hydrochloride in human liver microsomes. The extent of inhibition of metformin hydrochloride was assessed at concentrations of 0.1, 1, 10 and 100 μM. The following 13 test reactions were used as selective markers of the enzymatic activity of a single or two closely related cytochrome P450 isoenzymes that are relevant for drug metabolism in humans:

- phenacetin O-deethylation test for cytochrome P450 1A1 and 1A2
- coumarin 7-hydroxylation test for cytochrome P450 2A6
- bupropion hydroxylation test for cytochrome P450 2B6
- amodiaquine N-deethylation test for cytochrome P450 2C8
- diclofenac 4'-hydroxylation test for cytochrome P450 2C9
- flurbiprofen 4'-hydroxylation test for cytochrome P450 2C9
- S-mephenytoin 4'-hydroxylation test for cytochrome P450 2C19
- dextromethorphan O-deethylation test for cytochrome P450 2D6
- lauric acid 11-hydroxylation test for cytochrome P450 2E1
- nifedipine oxidation test for cytochrome P450 3A4
- testosterone 6β-hydroxylation test for cytochrome P450 3A4
- midazolam 1'-hydroxylation test for cytochrome P450 3A4
- lauric acid 12-hydroxylation test for cytochrome P450 4A11

The test substrates were incubated with human liver microsomes in the presence of β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) and the formation of the respective metabolites was quantified using sensitive and selective analytical techniques. Metformin hydrochloride was added to the incubation experiments and its effect on the formation of the respective metabolites was evaluated.

The results showed that:

- No pronounced inhibition of the various test reactions by metformin hydrochloride was observed (IC50 values >100 μM).
- There was no indication of a mechanism-based inhibition of CYP 3A4 by metformin hydrochloride.

Therefore, metabolic drug-drug interactions, based on inhibition of CYP enzymes by metformin hydrochloride, with other drugs that are substrates of CYP enzymes are unlikely to occur.

2.4.2.3 What is the mutual effect of co-administration of linagliptin and metformin on the pharmacokinetics of both drugs?

The dedicated DDI study was reviewed under NDA 201280 (see clinical Pharmacology review dated 03/08/2011 in DAARTS). In brief, co-administration of multiple daily doses of linagliptin 10 mg (supratherapeutic) with metformin (850 mg 3 times daily), an organic cationic transporter (OCT) substrate, did not meaningfully alter the pharmacokinetics of either linagliptin or metformin in healthy volunteers.

2.4.2.2 What is the effect of Trade® co-administration on the pharmacokinetics of other drugs?

Pharmacokinetic drug interaction studies with Trade® have not been performed; however, such studies have been conducted with the individual components of Trade® (linagliptin and metformin HCL) and have been reviewed in the respective NDAs. However, the application of results of DDI evaluation observed independently for the individual components to the Trade® use is summarized below in Table 6:

Table 6 DDI assessment for Trade® formulation during the development

Evaluation	**Is there any clinically meaningful effect on either linagliptin or the drug in question?**	**Is there any clinically meaningful effect on either metformin or the drug in question?**	**Implications for Lina/Met FDC**
Oral Contraceptives: levonorgestrel and ethinylestradiol	None	No information	None
SUs: glyburide (or glipizide, tolbutamide, and glimepiride)	None	None	None
Pioglitazone:	None	None (based on pioglitazone label)	None
Digoxin (Apply to other cationic drugs: amiloride, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin)	None	May interact	Use with caution
Warfarin	None	No information	None
Simvastatin	None	Not expected mechanistically	None
Ritonavir	None	Not expected mechanistically	None

(Table 6 Continued)

Evaluation	**Is there any clinically meaningful effect on either linagliptin or the drug in question?**	**Is there any clinically meaningful effect on either metformin or the drug in question?**	**Implications for Lina/Met FDC**
Rifampin	Yes, reduced linagliptin exposure, could be associated with reduced efficacy	Uncertain [based on DDI study Cho SK, Clin Pharmacol Ther. 2011 Mar; 89(3):416-21. Epub 2011 Jan 26]	Do not use with Rifampin (as per Tradjenta® label)
Furosemide	Not evaluated (Not expected mechanistically)	None	None
Nifedipine	Not evaluated (Not expected mechanistically)	None	None
Cimetidine	Not evaluated (Not expected mechanistically)	Yes, 60% higher Cmax, 40% higher AUC of metformin	Caution, patient monitoring, adjust Trade® dose if necessary
Propranolol	Not evaluated (Not expected mechanistically)	None	None
Ibuprofen	Not evaluated (Not expected mechanistically)	None	None

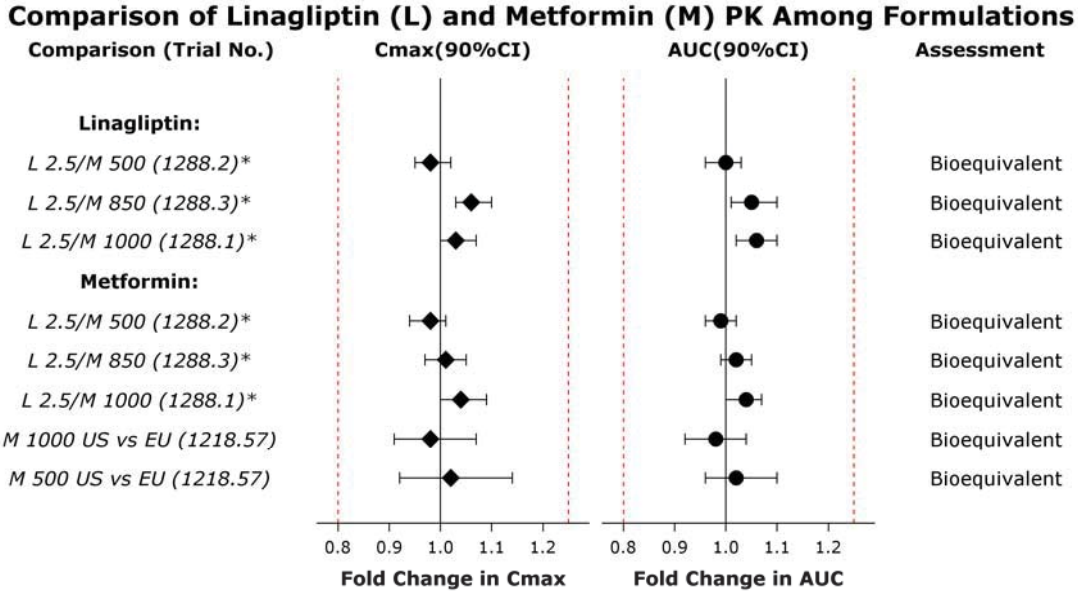
2.5 General Biopharmaceutics

2.5.1 Is bioequivalence established between the to-be-marketed formulation and the Phase 3 formulations and how does it relate to the overall product development?

A single, well-controlled Phase 3 Trial 1218.46 was conducted to support the linagliptin / metformin FDC tablets. In this trial single entity tablets linagliptin (2.5 mg and 5 mg tablets) and metformin (Glucophage® 500 and 1000 mg – EU commercial tablets) and the corresponding placebo formulations were used. Therein the efficacy/safety of therapeutic mechanisms was evaluated for the lower dose strength of Lina 2.5+Met 500 mg and the higher dose strength of Lina 2.5 +Met 1000 mg, bracketing the intermediate dose strength of Lina 2.5+Met 850 mg.

Bioequivalence of the single entity tablets used in the Phase 3 Trial 1218.46 compared to the fixed dose combination tablets that are to be marketed was evaluated in two bioequivalence studies. Study 1288.2 evaluated bioequivalence of the lowest FDC dose strength (Lina 2.5/Met 500 mg) to the respective single entity tablets, and Study 1288.1 evaluated bioequivalence of the proposed highest FDC dose strength (Lina 2.5/Met 1000 mg) to the respective single entity tablets. In addition, Study 1288.3 evaluated bioequivalence of the single entity tablets and the intermediate FDC dose strength (Lina 2.5/Met 850 mg). The bioequivalence of the European commercial metformin innovator product, which was used in the pivotal Phase 3 Study 1218.46, compared to the US commercial metformin innovator product was evaluated in Study 1218.57 at dose strengths of 500 and 1000 mg. Summary of various bioequivalence assessments carried out for Trade® formulation is presented in Figure 10. As shown, both linagliptin and metformin components from the FDC were bioequivalent to the individual drugs administered together.

Figure 10 Summary of BE evaluations conducted for the formulations utilized during clinical development including the intended commercial formulation

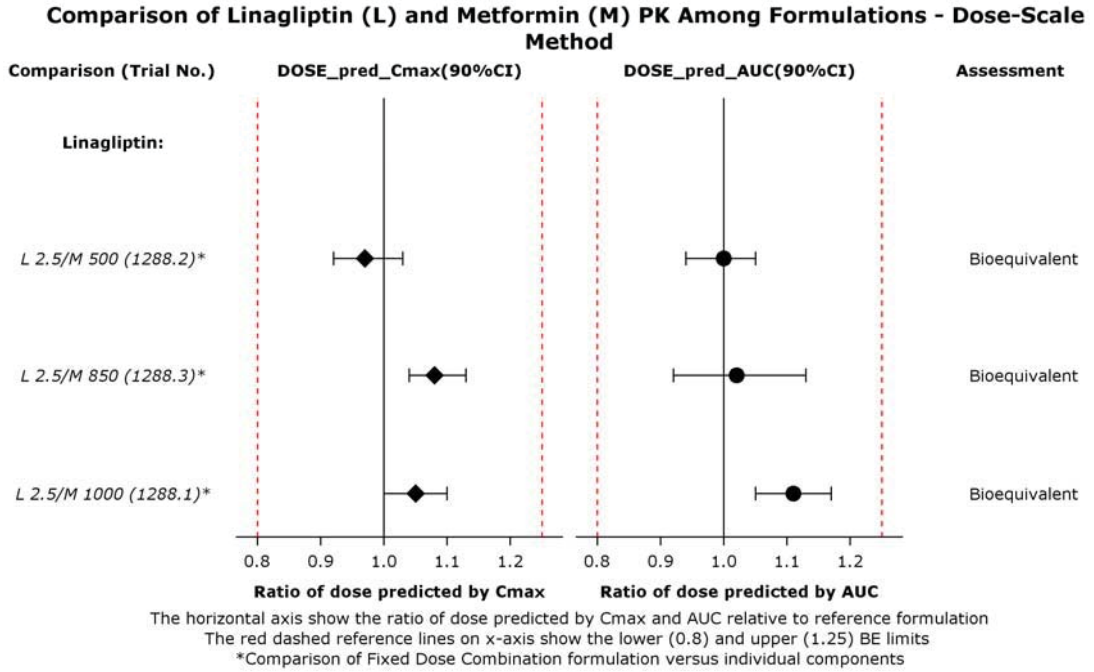


Linagliptin has nonlinear pharmacokinetics with less than proportional increase in exposure over the dose range of 1 to 10 mg. During the developmental stage sponsor was advised to evaluate the BE using the dose-scale method as secondary analysis. Sponsor, however, conducted traditional

BE analysis and supported it with the rational that the AUC is more appropriate measure than the bioavailable dose (predicted by the model). Though they did conduct dose scale assessment, using the power model derived from a Phase 1 single rising dose PK study conducted under linagliptin NDA. Sponsor's modeling results show that back-calculation from the exposure level to the dose level leads to larger relative differences on the dose level. The analysis showed that the AUC range following 4 mg (80% of 5 mg) and 6.25 mg (125% of 5 mg) corresponds to 87.9% and 113.8%, respectively, of AUC following 5 mg linagliptin. Similarly, the Cmax range following 4 mg and 6.25 mg linagliptin corresponds to 85.9% and 116.5%, respectively, of Cmax following 5 mg. On the other hand, 80% and 125% of AUC following 5 mg corresponds to the dose range of 3.40 mg (68.0% of 5 mg) and 7.36 mg (147.1% of 5 mg), respectively. Similarly, 80% and 125% of Cmax following 5 mg corresponds to the dose range of 3.61 mg (72.1% of 5 mg) and 6.93 mg (138.6% of 5 mg), respectively.

In this reviewer's own analysis, the sponsor's power model estimates (both Cmax and AUC) were utilized to back calculate the dose level from the observed Cmax and AUC values for the three BE trials. The predicted dose for test and reference treatments were compared using the traditional BE analysis in SAS. The results of bioequivalence assessments based on the predicted dose for the BE trials is presented in Figure 11. The results of this analysis further support the BE claim from the conventional analysis (Figure 10).

Figure 11 Summary of BE evaluations conducted using the predicted dose for the intended commercial formulation



Based on the results of statistical analyses of the PK parameters it can be concluded that:

- Both Lina 2.5 mg/Met 500 mg and Lina 2.5 mg/Met 1000 mg FDC formulations demonstrate bioequivalence to the co-administered individual components used in the Phase 3 trial.
- Lina 2.5 mg/Met 850 mg FDC formulation demonstrate bioequivalence to the co-administered individual components.

- The US and EU sourced metformin formulations were also bioequivalent when compared at 500 mg and 1000 mg dose strengths.

The DSI inspection results for two of the pivotal BE trials (1288.1 and 1218.57) revealed that there is no issues with regards to integrity of trial and bioanalytical data. The issues identified during the inspection were either minor or appropriately resolved.

2.6 Analytical

2.6.1 Is the analytical method for quantitation of linagliptin and metformin in human plasma appropriately validated?

Yes, the bioanalytical methods for quantitation of linagliptin and metformin in human plasma samples obtained from clinical pharmacology and safety/efficacy studies as reported by the sponsor are adequate. The analytes were quantitated using high performance liquid chromatographic (HPLC) mass spectrometry (LC/MS/MS) methods.

An overview of the various assays used for each clinical study is presented below in Table 7.

Table 7 Summary of analytical method used for the CPB studies

Study	Type	Analytes	Lab[1]
1218.4	DDI metformin	Linagliptin/ metformin	BI/ (b) (4)
1218.45	PK/PD of linagliptin 5 mg qd vs. 2.5 mg bid	Linagliptin/ metformin	(b) (4)
1218.46	Fact. design free combo linagliptin + metformin	Linagliptin/ metformin	
1218.47	Pilot BA linagliptin 2.5+metformin 1000	Linagliptin/ metformin	
1218.57	US vs. EU Glucophage	Metformin	
1288.1	Pivotal BE FDC 2.5/1000	Linagliptin/ metformin	
1288.2	Pivotal BE linagliptin 2.5+metformin 500	Linagliptin/ metformin	
1288.3	Pivotal BE linagliptin 2.5+metformin 850	Linagliptin/ metformin	
1288.4	Food Study FDC linagliptin 2.5+metformin 1000	Linagliptin/ metformin	

BI= Boehringer Ingelheim; (b) (4)

1. Analysis of Linagliptin in Human Plasma

An HPLC-MS/MS method for the quantification of linagliptin was developed and validated for the human biological matrix plasma to support the clinical linagliptin / metformin combination development program. Initially the assay was developed at BI for linagliptin only and afterwards modified for a simultaneous determination of linagliptin and its metabolite CD 1790. The assay for the simultaneous quantification of linagliptin and its main metabolite CD 1790 was transferred to (b) (4) and cross validated. In the BI and (b) (4) methods, samples were extracted by solid phase extraction and analyzed on a reversed phase column in gradient mode with MS/MS detection. Concentration ranges were from 0.529 to 529 nmol/L and from 0.100 to 1000 nmol/L for linagliptin. A calibration range in plasma from 0.100 to 20.0 nmol/L for linagliptin better reflected the anticipated drug concentrations of the therapeutic 5 mg linagliptin dose, was also successfully revalidated during clinical Trial 1218.31. Depending on the method, different amounts of plasma (linagliptin only method: plasma 50 µL, linagliptin/CD 1790 method: plasma 150 µL) were aliquoted and [$^{13}C_3$]-linagliptin was added as internal standard. Samples were extracted by solid-phase extraction on mixed-mode 96-well plates. Extracts were chromatographed on an analytical reversed phase column in gradient mode. For the quantification of linagliptin and its internal standard, the precursor to product transitions of m/z = 473 → 420 and m/z = 476 → 423 were monitored.
Linagliptin proved to be stable in human plasma under all conditions tested, e.g., throughout 3 freeze-thaw cycles, for at least 24 hours at room temperature and for at least 13 months (416 days in plasma) in the freezer, which covered the maximum storage time of plasma samples from clinical studies.

2. Analysis of Metformin in Human Plasma

An HPLC-MS/MS method for the quantification of metformin was developed and validated for the human biological matrix plasma to support the clinical linagliptin / metformin combination development program. The assay was validated at (b) (4). In brief, samples were extracted by solid phase extraction and analyzed on a reversed phase column in gradient mode with MS/MS detection. Concentration ranges were from 5.00 to 2500 ng/mL. 50 µL plasma was aliquoted and [D6] metformin was added as internal standard. Samples were extracted by solid-phase extraction on mixed-mode 96-well plates. Extracts were chromatographed on an analytical reversed phase column in gradient mode. For the quantification of metformin and its internal standard, the precursor to product transitions of m/z = 130 → 71 and m/z = 136 → 77 were monitored.

Metformin was found to be stable in human plasma under all conditions tested, e.g., throughout 3 freeze-thaw cycles, for at least 4 hours at room temperature and for at least 6 months (201 days in plasma) in the freezer, which covered the maximum storage time of plasma samples from clinical studies.

3. Mutual Interference in Linagliptin and Metformin Assay in Human Plasma

Sponsor also tested the interference of metformin on the ion trace of linagliptin and the interference of linagliptin on the ion trace of metformin. The selectivity of the analytical method of metformin against linagliptin was demonstrated during Study 1218.4. This selectivity test was performed by testing for metformin using blank plasma samples spiked with 21.2 nmol/L linagliptin. The selectivity of the analytical method of linagliptin against metformin was demonstrated during Study 1218.47. This selectivity test was performed by testing for linagliptin

using blank plasma samples spiked at 2000 ng/mL with metformin. No mutual interference was observed during the quantiation of linagliptin and metformin assays.

These results indicated that the intra-day and inter-day precision and accuracy were satisfactory for determination of linagliptin and metformin in human plasma and the methods were adequately validated. The analytical ranges for these analytes (including the dilution factors) used were sufficient to cover the observed concentrations in the clinical studies.

An overview of the performance of various assays is presented below in Table 8:

Table 8 Performance summary of analytical methods used for the CPB studies to quantitated linagliptin in human plasma

BI, Biberach, Germany	LLOQ	QC_low	QC_mid	QC_high
Range: 0.250 - 250 ng/mL	0.529 nM (0.250 ng/mL)	1.32 nM (0.625 ng/mL)	26.4 nM (12.5 ng/mL)	423 nM (200 ng/mL)
Inaccuracy (%)	0.5	3.6	5.5	-4.6
Imprecision (%)	6.2	3	1.2	1.9
N	18	10	10	10
BI, Biberach, Germany				
Range: 0.100 - 100 nmol/L	0.100 nmol/L	0.250 nmol/L	5.00 nmol/L	80.0 nmol/L
Inaccuracy (%)	5.2	6.5	5.9	-0.7
Imprecision (%)	7.5	3.4	1.7	1.5
N	17	10	9	10
(b) (4)				
Range: 0.100 - 100 nmol/L	0.100 nmol/L	0.250 nmol/L	5.00 nmol/L	80.0 nmol/ L
Inaccuracy (%)	0	0.4	4.4	-3.4
Imprecision (%)	5.4	3.6	1.9	1.8
N	18	10	10	10

Abbreviations: N=number, QC = quality control

Table 9 Performance summary of metformin analytical method used for the CPB studies (Assay validation performed at (b) (4) (b) (4))

	LLOQ	QC_low	QC_mid	QC_high
Matrix: Human plasma	[ng/mL]	[ng/mL]	[ng/mL]	[ng/mL]
Range: 5.00-2500 ng/mL	5	10	1000	2000
Inaccuracy (%)	4	1	2	0
Imprecision (%)	5.5	2.7	1.9	1.7
N	18	6	6	6

Abbreviations: N=number, QC = quality control

3 Labeling Comments

Note: Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Proposed Text:

7.2 Drug Interactions with Linagliptin

Inducers of P-glycoprotein and CYP3A4 Enzymes

Rifampin decreased linagliptin exposure; suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. (b) (4) use of alternative treatments is strongly recommended (b) (4) [see Clinical Pharmacology (12.3)].

8.5 Geriatric Use

Linagliptin is minimally excreted by the kidney; however, (b) (4) metformin is substantially excreted by the kidney. (b) (4) (b) (4) aging can be associated with reduced renal function, TRADE should be used with caution as age increases [see Warnings and Precautions (5.1, 5.2) and Clinical Pharmacology (12.3)].

Linagliptin

Of the total number of patients (n = 4040) in clinical studies of linagliptin, 1085 patients were 65 years and over, while 131 patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in elderly population. While clinical studies of linagliptin (b) (4) have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. (b) (4)

10 OVERDOSAGE

Linagliptin

During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of linagliptin (equivalent to 120 times the recommended daily dose) there were no dose related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

In the event of an overdose, contact the Poison Control Center. (b) (4) Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of l(b) (4)inagliptin (b) (4) (b) (4) by hemodialysis or peritoneal dialysis is unlikely.

12.3 Pharmacokinetics

Absorption

(b) (4)

Administration of linagliptin 2.5 mg/metformin hydrochloride (b) (4) fixed-dose combination with food resulted in no change in overall exposure of linagliptin. There was no change in metformin AUC, however, mean peak serum concentration of metformin was decreased by 1(b) (4)8% when administered with food. A delayed time-to-peak serum concentrations by 2(4) hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant.

Linagliptin
The absolute (b) (4) bioavailability of linagliptin is approximately 30%. (b) (4)

Metformin
The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. (b) (4)

Distribution

Metformin

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Specific Populations

Renal Impairment

TRADE: Use of TRADE is contraindicated (b) (4) in patients with renal impairment (e.g., serum creatinine ≥1.5 mg/dL [males] or ≥1.4 mg/dL [females], or abnormal creatinine clearance) [see Contraindications (4) and Warnings and Precautions (5.2)].

Metformin: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. [See

Contraindications (4) and Warnings and Precautions (5.2) [redacted] (b) (4)

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment[redacted] (b) (4). Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore, use of TRADE is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.4)]*.

20 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

4.2 Individual Study Reviews

[**Note**: *For the individual study reviews for BE and the food effect study, the results are based on reviewer's PK analysis of data. The sponsor used AUC0-inf, predicted (pre-specified end point in the statistical analysis plan) instead of AUC0-inf, observed (recommended in the FDA Guidance document for Bioequivalence Assessment) for metformin. The reviewer's analysis focused on both AUC0-t and AUC0-inf, observed for the total exposure part*]

4.2.1 BE Study (1218.1)

This study was a pivotal BE study comparing the intended commercial FDC formulation containing 2.5 mg linagliptin and 1000 mg metformin in a film coated, immediate release tablet to the co-administration of individual formulations used in the Phase 3 trial.

The study design is as follows:

<table>
<tr><td>Title:</td><td>Bioequivalence of a 2.5 mg linagliptin / 1000 mg metformin fixed-dose combination tablet compared with single linagliptin 2.5 mg and metformin 1000 mg tablets administered together in healthy male and female volunteers (an open-label, randomized, single dose, two-way crossover, Phase I trial)</td></tr>
<tr><td>Objectives:</td><td>Primary: To demonstrate bioequivalence of a 2.5 mg linagliptin/1000 mg metformin fixed-dose combination (FDC) tablet compared with single tablets of linagliptin 2.5 mg and metformin 1000 mg administered together.</td></tr>
<tr><td>Study Design</td><td>Study was conducted as an open-label, randomized, single-dose, 2-way crossover design. The 2 study treatments (A and B) were as follows:

A = Linagliptin 2.5 mg/Metformin 1000 mg FDC Tablet (Test)
B = One Linagliptin 2.5 mg + One Glucophage® 1000 mg Tablet (Reference)

Following a fast of at least 10 hours, subjects received a single oral dose of study drug on Day 1 of each treatment period. The 2 treatments were separated by a washout period of at least 35 days.</td></tr>
<tr><td>Study Population</td><td>N= 96 Healthy subjects, Gender: 62 M and 34F, Age: 35 (18-54) yr, BMI: 24 (19-30) kg/m^2</td></tr>
<tr><td>Investigational Products:</td><td>
<table>
<tr><td></td><td>Treatment A (test)
FDC</td><td colspan="2">Treatment B (reference)
single tablets</td></tr>
<tr><td>Substance</td><td>Linagliptin/metformin</td><td>Linagliptin</td><td>Metformin (Glucophage®)</td></tr>
<tr><td>Pharmaceutical form</td><td>FDC tablet</td><td>Tablet</td><td>Tablet</td></tr>
<tr><td>Unit strength</td><td>2.5 mg linagliptin
1000 mg metformin</td><td>2.5 mg linagliptin</td><td>1000 mg metformin</td></tr>
<tr><td>Posology</td><td>Single dose</td><td>Single dose</td><td>Single dose</td></tr>
<tr><td>Route of administration</td><td>Oral</td><td>Oral</td><td>Oral</td></tr>
<tr><td>Source</td><td>BI Pharma GmbH & Co. KG</td><td>BI Pharma GmbH & Co. KG</td><td>Merck Pharma GmbH</td></tr>
<tr><td>Batch no.</td><td>903235</td><td>B081004241</td><td>X1444 Merck Pharma GmbH</td></tr>
</table>
</td></tr>
<tr><td>Sampling: Blood</td><td>Blood samples for determination of linagliptin and metformin plasma</td></tr>
</table>

	concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (0 hour), and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 11, 12, 24, 34, 48, and 72 hours post-dose. Linagliptin accumulation half-life (t1/2) is approximately 8-12 hr, metformin has a t1/2 of approximately 6 hr; thus, a 72-h plasma concentration versus time profiling appears to be adequate for both analytes.
Urine	none
Feces	none
PK Assessments	AUC0-72 (linagliptin), AUC0-t, AUC%extrapolated, AUC0-∞, Cmax, Tmax, Kel, t1/2
Primary endpoints:	AUC0-72 and Cmax for linagliptin; AUC0-∞ and Cmax for metformin
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	None

Protocol Deviations: Subject 11 was excluded from the per-protocol set for evaluation of bioequivalence (PPS-BE; see Section 11.1) because of vomiting after single tablets treatment, which occurred before 2-times median tmax (3h). Subject 89 was excluded from the PPS-BE due to intake of the forbidden antibiotic azithromycin (daily dose of 500 mg) as late as 96 h prior to the second treatment period (single tablets). Azithromycin has a half-life of about 70 h and is known to inhibit P-gp, a major determinant of linagliptin kinetics.

Subject Disposition and Data Sets Analyzed:
No. of subjects planned: 96
Actual who entered: 96
Treatment A (FDC tablet): Treated: 96, analyzed (for primary endpoints): 96
Treatment B (single tablets): Treated: 95, analyzed (for primary endpoints): 93.

Bioanalytical Results:
Linagliptin (b) (4)***:*** The calibration curve of undiluted plasma samples was linear over the range of concentrations from 0.100 to 20.0 nmol/L for BI 1356 BS. The performance summary of analytical method during sample analysis is presented below:

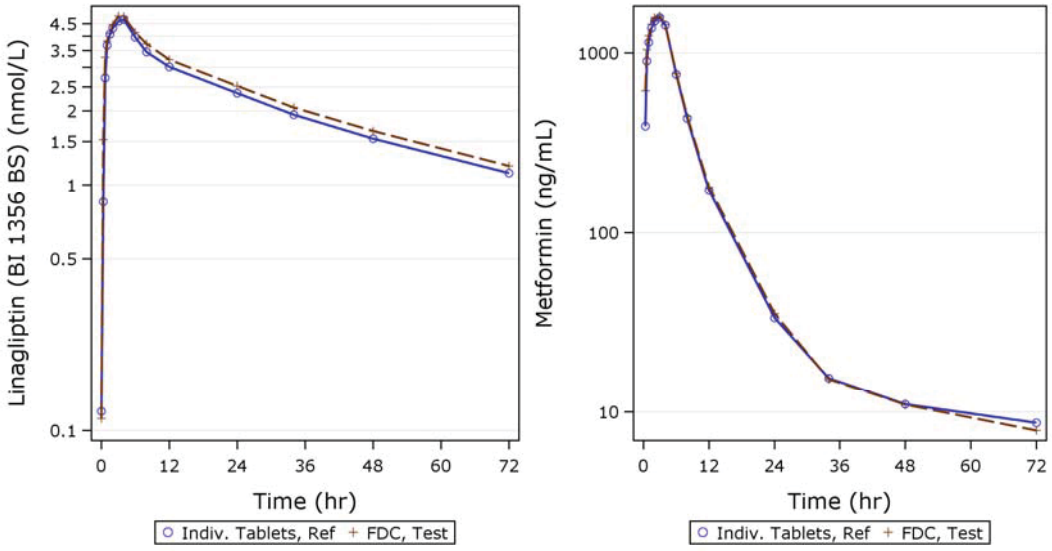
Analyte: linagliptin	Label	Nominal concentration (nmol/L)	N	Inaccuracy (%)	Imprecision (RSD%)
	LoQC	0.250	67	0.8	9.9
	MeQC	1.00	67	2.0	5.3
	HiQC	15.0	67	-2.7	3.7

Metformin (b) (4)***:*** The analytical procedure in human plasma was shown to be linear from 5.00 to 2500 ng/mL (weighting factor 1/x) using 50 µL of sample for metformin. The performance summary of analytical method during sample analysis is presented below:

Analyte: Metformin	Name	Concentration (ng/ml)	N	Inaccuracy (%)	Imprecision (RSD%)
	QC.LOW	10.0	55	-4.2	4.7
	QC.MID	1000	55	-1.2	5.2
	QC.HIGH	2000	56	-0.5	3.3

Pharmacokinetic Results:

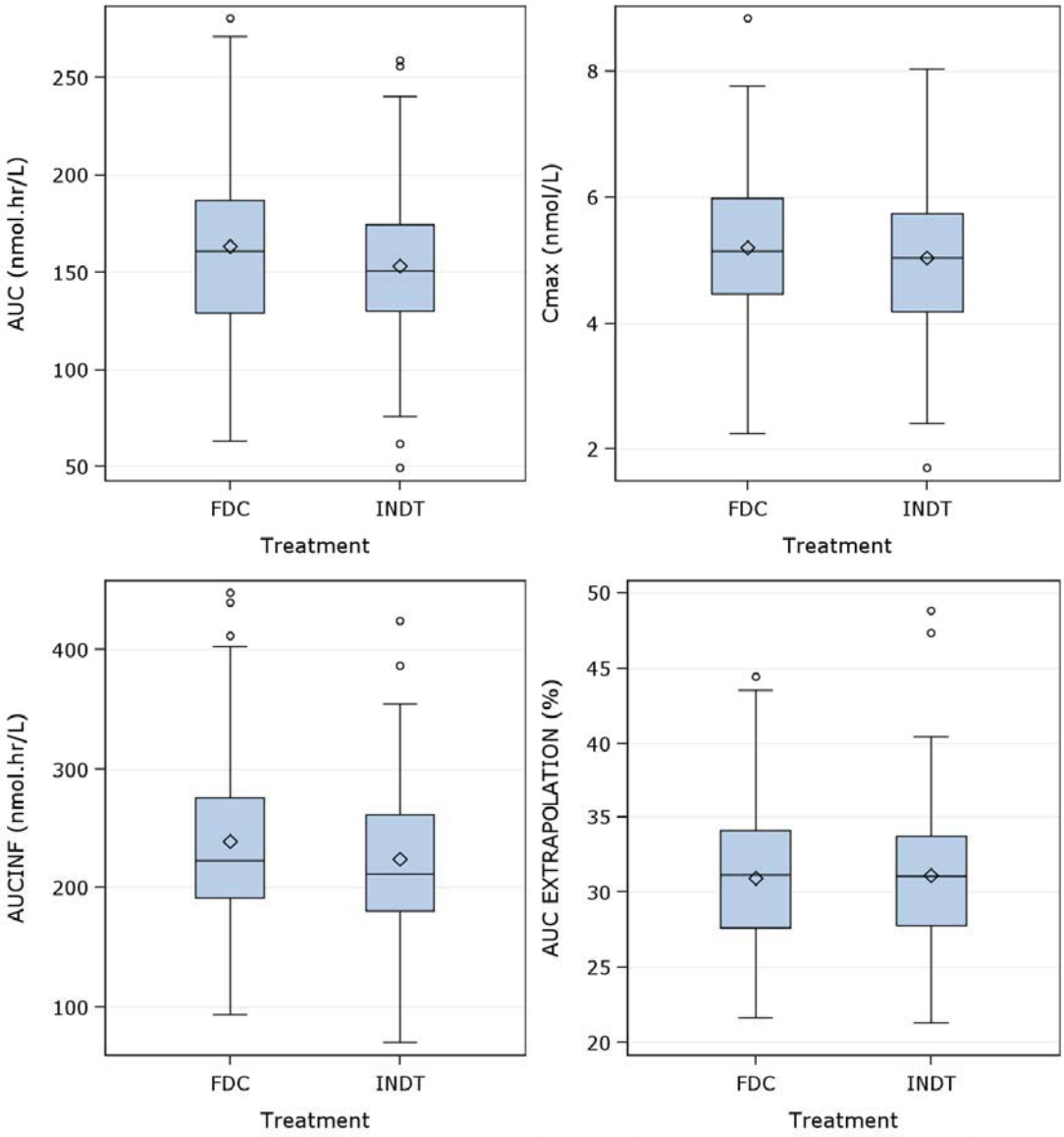
The mean concentration-time profiles of linagliptin and metformin by treatment are shown in Figure below:



Mean Concentration-time Plots by Treatment (Trial 1288.1) Lina 2.5 mg/Met 1000 mg

The distribution of PK parameters by treatment for linagliptin and metformin is summarized in the figures below:

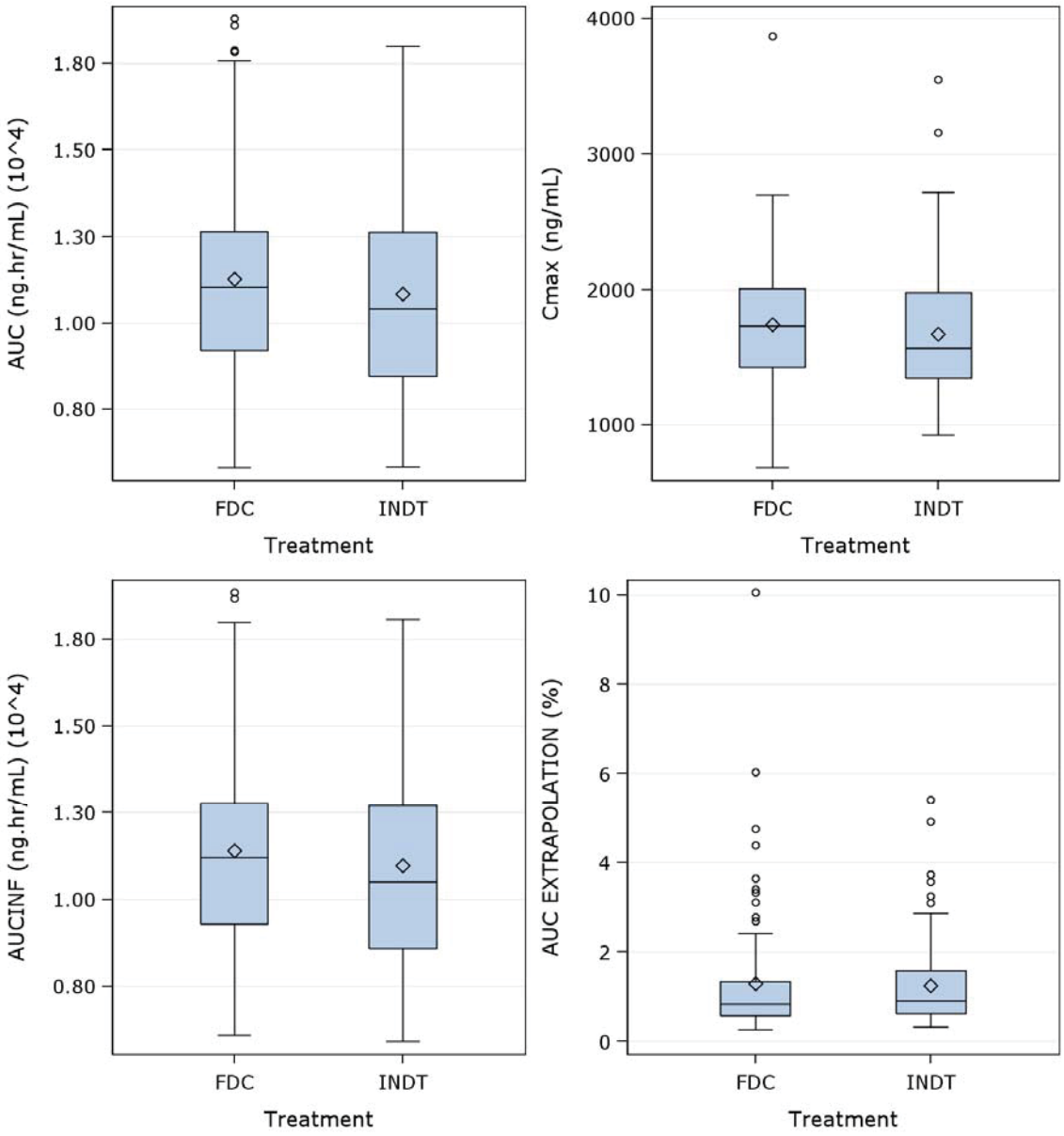
Linagliptin:



Treatment FDC= L 2.5/M 1000 mg FDC Tablet (Test) INDT= Individual Tablets (Ref)

Linagliptin (BI 1356 BS) PK parameters by treatment (Trial 1288.1)

Metformin:



Treatment FDC= L 2.5/M 1000 mg FDC Tablet (Test) INDT= Individual Tablets (Ref)

Metformin PK parameters by treatment (Trial 1288.1)

The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both linagliptin and metformin. Although, for linagliptin AUC0-72 h was used as primary parameter as % extrapolated is in excess of 10%.

The geometric mean ratios and 90% CIs from the statistical comparison of PK parameters are presented in the following tables.

Table 1 Statistical comparison for linagliptin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
FDC	INDT	AUC(0-inf)_Obs	nmol.hr/L	105.73	101.67 - 109.96
		AUC(0-inf)_Pred	nmol.hr/L	105.83	101.72 - 110.1
		AUC(0-t)	nmol.hr/L	106.38	102.7 - 110.18
		Cmax	nmol/L	103.44	100.29 - 106.68
		Pred_Dose_AUC	mg	110.98	104.98 - 117.32
		Pred_Dose_CMAX	mg	105.07	100.43 - 109.93
FDC = Fixed Dose Combination Tablet L/M 2.5/1000 mg INDT = Individual Linagliptin Tablet 2.5 mg					

t= 72 hr for AUC0-t.

Table 2 Statistical comparison for metformin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
FDC	INDT	AUC(0-inf)_Obs	ng.hr/mL	103.64	100.11 - 107.29
		AUC(0-inf)_Pred	ng.hr/mL	103.63	100.1 - 107.28
		AUC(0-t)	ng.hr/mL	103.62	100.02 - 107.35
		Cmax	ng/mL	104.26	99.84 - 108.87
FDC = Fixed Dose Combination Tablet L/M 2.5/1000 mg INDT = Individual Metformin Tablet 1000 mg					

t= 72 hr for AUC0-t.

Conclusions:
The design and conduct of Trial 1288.1 are reasonable from a clinical pharmacology perspective. The protocol deviations are handled appropriately. The bioanalytical methods, as reported, adequately support the trial results. The results of the Trial 1288.1 demonstrate that the Lina 2.5/Met 1000 mg FDC formulation is bioequivalent to single co-administration of Lina 2.5 mg and Glucophage® 1000 mg tablets, for both linagliptin and metformin total and peak exposures.

4.2.2 BE Study (1218.2)

This study was a pivotal BE study comparing the intended commercial FDC formulation containing 2.5 mg linagliptin and 500 mg metformin in a film coated, immediate release tablet to the co-administration of individual formulations used in the Phase 3 trial.
The study design is as follows:

<table>
<tr><td>Title:</td><td colspan="3">Bioequivalence of a 2.5 mg linagliptin / 500 mg metformin fixed dose combination tablet compared with single linagliptin 2.5 mg and metformin 500 mg tablets administered together in healthy male and female volunteers (an open-label, randomized, single dose, two-way crossover, Phase I trial)</td></tr>
<tr><td>Objectives:</td><td colspan="3">Primary: To demonstrate bioequivalence of a 2.5 mg linagliptin/500 mg metformin fixed-dose combination (FDC) tablet compared with single tablets of linagliptin 2.5 mg and metformin 500 mg administered together.</td></tr>
<tr><td>Study Design</td><td colspan="3">Study was conducted as an open-label, randomized, single-dose, 2-way crossover design. The 2 study treatments (A and B) were as follows:

A = Linagliptin 2.5 mg/Metformin 500 mg FDC Tablet (Test)
B = One Linagliptin 2.5 mg + One Glucophage® 500 mg Tablet (Reference)

Following a fast of at least 10 hours, subjects received a single oral dose of study drug on Day 1 of each treatment period. The 2 treatments were separated by a washout period of at least 35 days.</td></tr>
<tr><td>Study Population</td><td colspan="3">N= 95 Healthy subjects, Gender: 48 M and 47 F, Age: 36.5 (21-50) yr, BMI: 24 (19-30) kg/m^2</td></tr>
<tr><td>Investigational Products:</td><td></td><td>Treatment A (test)
FDC</td><td>Treatment B (reference)
Single tablets</td></tr>
<tr><td>Substance</td><td></td><td>Linagliptin/metformin</td><td>Linagliptin</td><td>Metformin (Glucophage®)</td></tr>
<tr><td>Pharmaceutical form</td><td></td><td>FDC tablet</td><td>Tablet</td><td>Tablet</td></tr>
<tr><td>Unit strength</td><td></td><td>2.5 mg linagliptin
500 mg metformin</td><td>2.5 mg linagliptin</td><td>500 mg metformin</td></tr>
<tr><td>Posology</td><td></td><td>Single dose</td><td>Single dose</td><td>Single dose</td></tr>
<tr><td>Route of administration</td><td></td><td>Oral</td><td>Oral</td><td>Oral</td></tr>
<tr><td>Source</td><td></td><td>BI Pharma GmbH & Co. KG</td><td>BI Pharma GmbH & Co. KG</td><td>Merck Pharma GmbH</td></tr>
<tr><td>Batch no.</td><td></td><td>902832</td><td>B081004241</td><td>250045</td></tr>
<tr><td>Sampling: Blood</td><td colspan="3">Blood samples for determination of linagliptin and metformin plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (0 hour), and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 11, 12, 24, 34, 48, and 72 hours post-dose.
Linagliptin accumulation half-life (t1/2) is approximately 8-12 hr, metformin has a t1/2 of approximately 6 hr; thus, a 72-h plasma concentration versus time profiling appears to be adequate for both analytes.</td></tr>
<tr><td>Urine</td><td colspan="3">none</td></tr>
<tr><td>Feces</td><td colspan="3">none</td></tr>
</table>

PK Assessments	AUC0-72 (linagliptin), AUC0-t, AUC%extrapolated, AUC0-∞, Cmax, Tmax, Kel, t1/2
Primary endpoints:	AUC0-72 and Cmax for linagliptin; AUC0-∞ and Cmax for metformin
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	None

Protocol Deviations: There was no important protocol violation in this study and there were no other major deviations from the study protocol.

Subject Disposition and Data Sets Analyzed:
No. of subjects planned: 96
Actual who entered: 95
Treatment A (FDC tablet): Treated: 94, analyzed (for primary endpoints): 94
Treatment B (single tablets): Treated: 95, analyzed (for primary endpoints): 95.

Bioanalytical Results:
Linagliptin (b) (4)**:** The calibration curve of undiluted plasma samples was linear over the range of concentrations from 0.100 to 20.0 nmol/L for BI 1356 BS. The performance summary of analytical method during sample analysis is presented below:

Linagliptin (BI 1356 BS)	Label	Nominal concentration [nmol/L]	N	Inaccuracy [%]	Imprecision [RSD%][1]
In-study	LoQC	0.250	68	-0.4	7.5
	MeQC	1.00	68	-0.4	4.9
	HiQC	15.0	68	-2.0	3.6

[1] Relative standard deviation

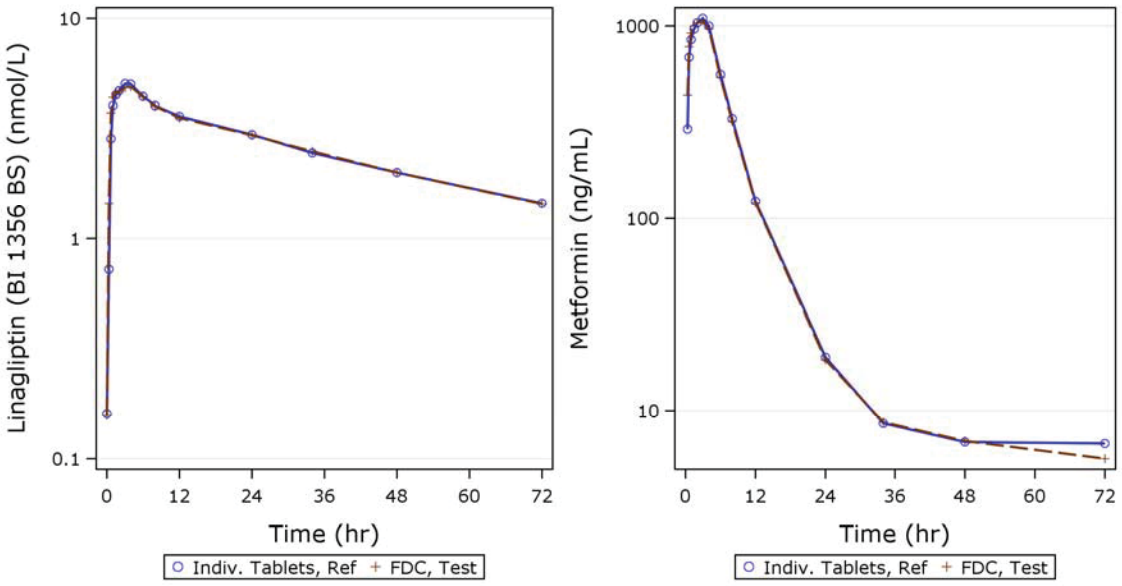
Metformin (b) (4) The analytical procedure in human plasma was shown to be linear from 5.00 to 2500 ng/mL (weighting factor 1/x) using 50 µL of sample for metformin. The performance summary of analytical method during sample analysis is presented below:

Metformin	Label	Concentration [ng/mL]	N	Inaccuracy [%]	Imprecision CV [%][1]
In-study	QC.LOW	10.0	56	-3.4	6.6
	QC.MID	1000	56	3.0	5.2
	QC.HIGH	2000	56	2.0	4.6

[1] Coefficient of variation

Pharmacokinetic Results:

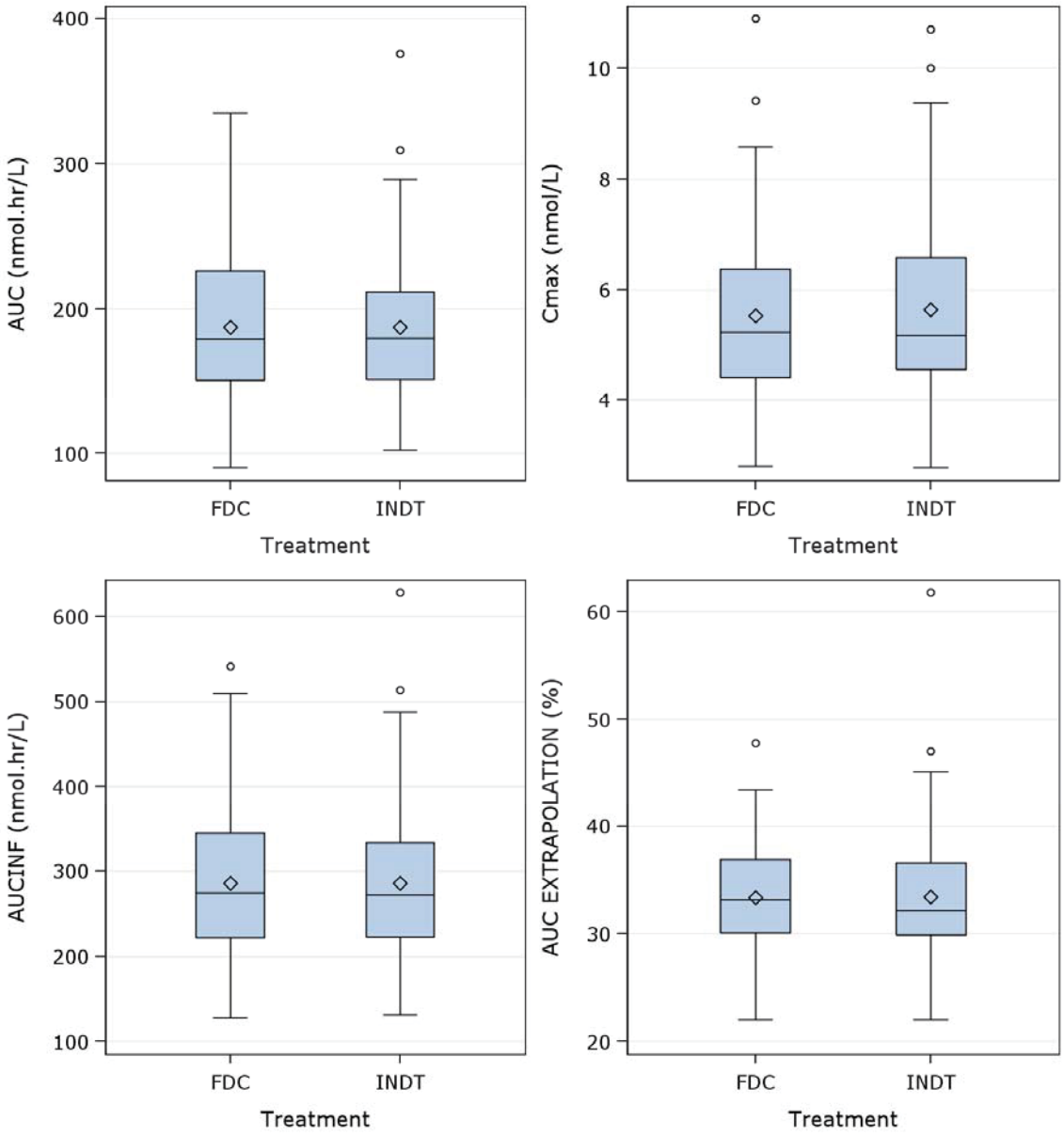
The mean concentration-time profiles of linagliptin and metformin by treatment are shown in Figure below:



Mean Concentration-time Plots by Treatment (Trial 1288.2) Lina 2.5 mg/Met 500 mg

The distribution of PK parameters by treatment for linagliptin and metformin is summarized in the figures below:

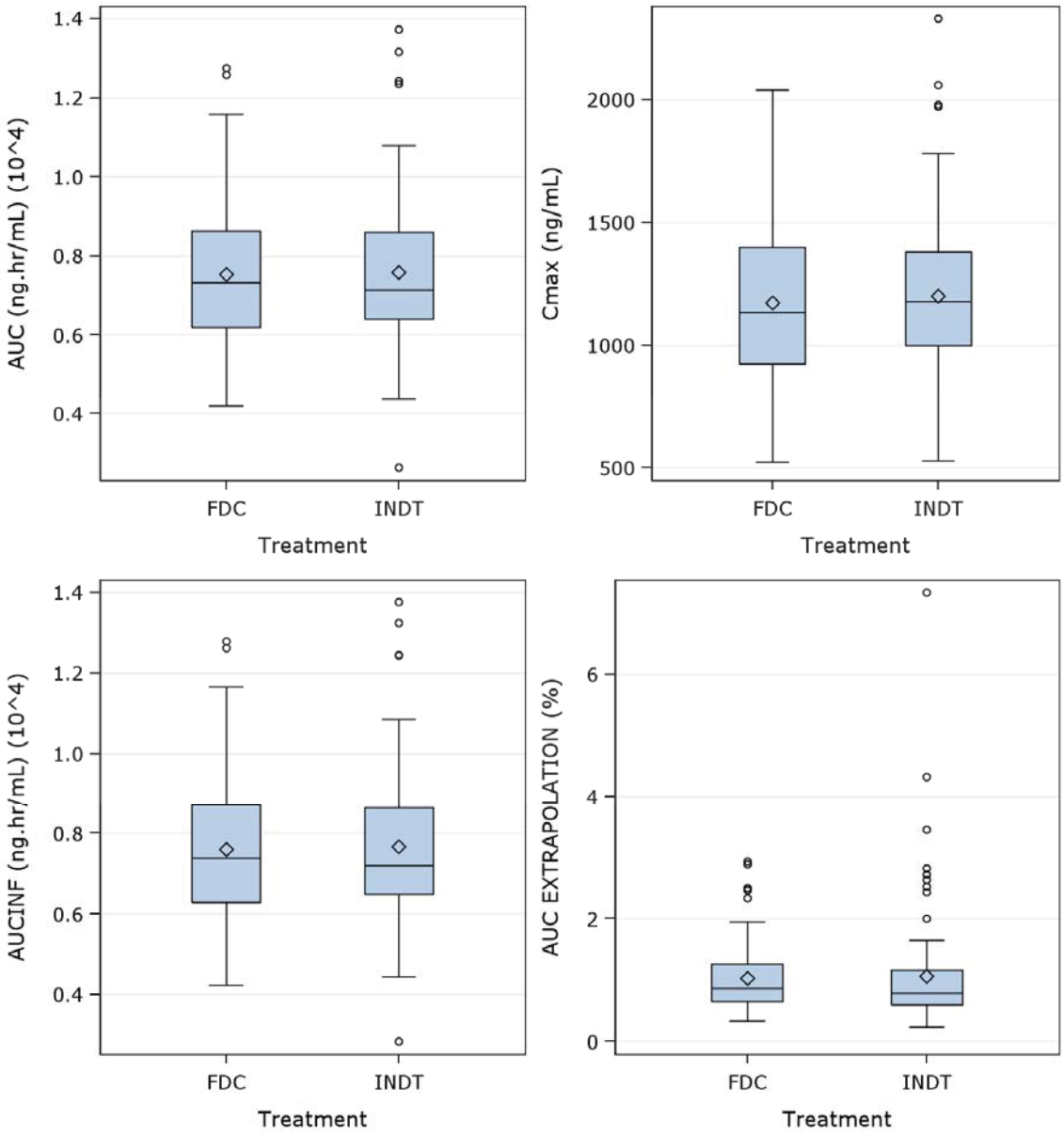
Linagliptin:



Treatment FDC= L 2.5/M 500 mg FDC Tablet (Test) INDT= Individual Tablets (Ref)

Linagliptin (BI 1356 BS) PK parameters by treatment (Trial 1288.2)

Metformin:



Treatment FDC= L 2.5/M 500 mg FDC Tablet (Test) INDT= Individual Tablets (Ref)

Metformin PK parameters by treatment (Trial 1288.2)

The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both linagliptin and metformin. Although, for linagliptin AUC0-72 h was used as primary parameter as % extrapolated is in excess of 10%.

The geometric mean ratios and 90% CIs from the statistical comparison of PK parameters are presented in the following tables.

Table 1 Statistical comparison for linagliptin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
FDC	INDT	AUC(0-inf)_Obs	nmol.hr/L	99.74	96.25 - 103.36
		AUC(0-inf)_Pred	nmol.hr/L	99.96	96.48 - 103.57
		AUC(0-t)	nmol.hr/L	99.92	96.63 - 103.33
		Cmax	nmol/L	98.22	94.51 - 102.07
		Pred_Dose_AUC	mg	99.55	94.08 - 105.34
		Pred_Dose_CMAX	mg	97.4	92.06 - 103.04
FDC = Fixed Dose Combination Tablet L/M 2.5/500 mg INDT = Individual Linagliptin Tablet 2.5 mg					

t= 72 hr for AUC0-t.

Table 2 Statistical comparison for metformin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
FDC	INDT	AUC(0-inf)_Obs	ng.hr/mL	99.27	96.45 - 102.18
		AUC(0-inf)_Pred	ng.hr/mL	99.3	96.46 - 102.22
		AUC(0-t)	ng.hr/mL	99.31	96.42 - 102.29
		Cmax	ng/mL	97.88	94.42 - 101.47
FDC = Fixed Dose Combination Tablet L/M 2.5/500 mg INDT = Individual Metformin Tablet 500 mg					

t= 72 hr for AUC0-t.

Conclusions:
The design and conduct of Trial 1288.2 are reasonable from a clinical pharmacology perspective. The protocol deviations are handled appropriately. The bioanalytical methods, as reported, adequately support the trial results. The results of the Trial 1288.2 demonstrate that the Lina 2.5/Met 500 mg FDC formulation is bioequivalent to single co-administration of Lina 2.5 mg and Glucophage® 500 mg tablets, for both linagliptin and metformin total and peak exposures.

4.2.3 BE Study (1218.3)

This study was a BE study comparing the intended commercial FDC formulation containing 2.5 mg linagliptin and 850 mg metformin in a film coated, immediate release tablet to the co-administration of individual formulations.

The study design is as follows:

<table>
<tr><td>Title:</td><td>Bioequivalence of a 2.5 mg linagliptin / 850 mg metformin fixed dose combination tablet compared with single linagliptin 2.5 mg and metformin 850 mg tablets administered together in healthy male and female volunteers (an open-label, randomized, single dose, two-way crossover, Phase I trial)</td></tr>
<tr><td>Objectives:</td><td>Primary: To demonstrate bioequivalence of a 2.5 mg linagliptin/850 mg metformin fixed-dose combination (FDC) tablet compared with single tablets of linagliptin 2.5 mg and metformin 850 mg administered together.</td></tr>
<tr><td>Study Design</td><td>Study was conducted as an open-label, randomized, single-dose, 2-way crossover design. The 2 study treatments (A and B) were as follows:

A = Linagliptin 2.5 mg/Metformin 850 mg FDC Tablet (Test)
B = One Linagliptin 2.5 mg + One Glucophage® 850 mg Tablet (Reference)

Following a fast of at least 10 hours, subjects received a single oral dose of study drug on Day 1 of each treatment period. The 2 treatments were separated by a washout period of at least 35 days.</td></tr>
<tr><td>Study Population</td><td>N= 95 Healthy subjects, Gender: 42 M and 54 F, Age: 37 (19-55) yr, BMI: 24 (19-29) kg/m^2</td></tr>
<tr><td>Investigational Products:</td><td>
<table>
<tr><td></td><td>Treatment A (test)
FDC</td><td colspan="2">Treatment B (reference)
Single tablets</td></tr>
<tr><td>Substance</td><td>Linagliptin/metformin</td><td>Linagliptin</td><td>Metformin (Glucophage®)</td></tr>
<tr><td>Pharmaceutical form</td><td>FDC tablet</td><td>Tablet</td><td>Tablet</td></tr>
<tr><td>Unit strength</td><td>2.5 mg linagliptin
850 mg metformin</td><td>2.5 mg linagliptin</td><td>850 mg metformin</td></tr>
<tr><td>Posology</td><td>Single dose</td><td>Single dose</td><td>Single dose</td></tr>
<tr><td>Route of administration</td><td>Oral</td><td>Oral</td><td>Oral</td></tr>
<tr><td>Source</td><td>BI Pharma GmbH
& Co. KG</td><td>BI Pharma GmbH
& Co. KG</td><td>Merck Pharma GmbH</td></tr>
<tr><td>Batch no.</td><td>902831</td><td>B081004241</td><td>X1486</td></tr>
</table>
</td></tr>
<tr><td>Sampling: Blood</td><td>Blood samples for determination of linagliptin and metformin plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (0 hour), and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 11, 12, 24, 34, 48, and 72 hours post-dose.
Linagliptin accumulation half-life (t1/2) is approximately 8-12 hr, metformin has a t1/2 of approximately 6 hr; thus, a 72-h plasma concentration versus time profiling appears to be adequate for both analytes.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
</table>

Feces	none
PK Assessments	AUC0-72 (linagliptin), AUC0-t, AUC%extrapolated, AUC0-∞, Cmax, Tmax, Kel, t1/2
Primary endpoints:	AUC0-72 and Cmax for linagliptin; AUC0-∞ and Cmax for metformin
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	None

Protocol Deviations: There was 1 important protocol violation in this study. A single linagliptin tablet was found in a used glass at the study site. When the bioanalytical results were available, the tablet could be assigned to Subject no. 72, as that was the only subject who showed no measurable plasma concentrations of linagliptin. The subject was excluded from the BE analysis.

Subject Disposition and Data Sets Analyzed:
No. of subjects planned: 96
Actual who entered: 96
Treatment A (FDC tablet): Treated: 96, analyzed (for primary endpoints): 95
Treatment B (single tablets): Treated: 96, analyzed (for primary endpoints): 94 (L)/93(M).

Bioanalytical Results:

Linagliptin (b) (4) ***:*** The calibration curve of undiluted samples was linear over the range of concentrations from 0.100 to 20.0 nmol/L for BI 1356 BS. The performance summary of analytical method during sample analysis is presented below:

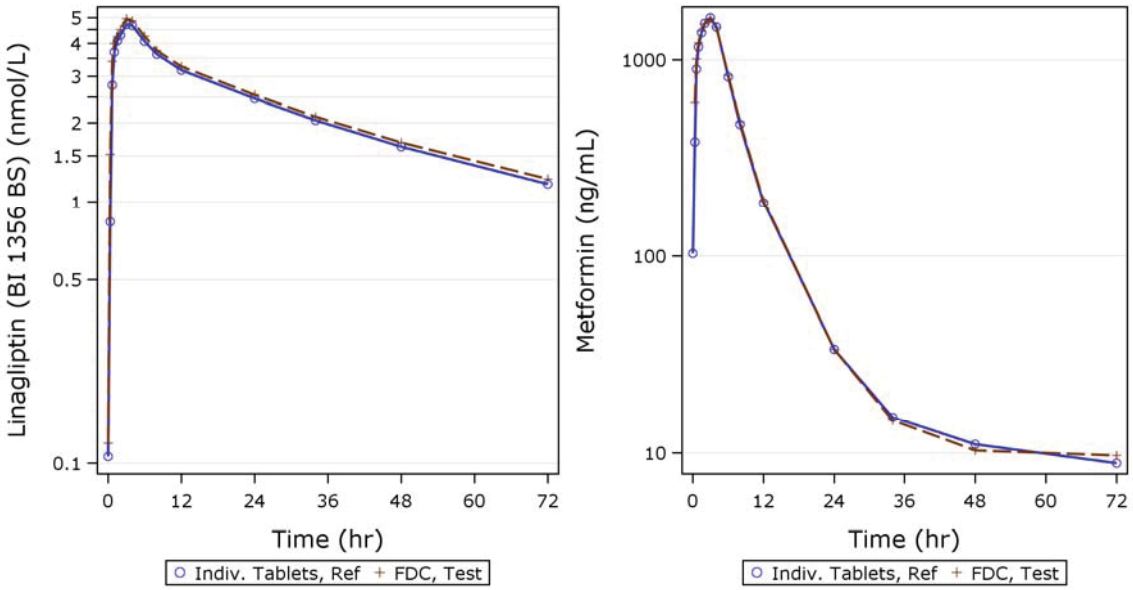
Analyte	Label	Nominal concentration [nmol/L]	N	Accuracy (%)	Precision RSD (%)
	LoQC	0.25	70	100	8.3
BI 1356 BS	MeQC	1	70	101	5.6
	HiQC	15	69	99.0	3.42

Metformin (b) (4) The calibration curve of undiluted samples was linear over the range of concentrations from 5 to 2500 ng/mL for metformin. The performance summary of analytical method during sample analysis is presented below:

Assay	Name	Concentration (ng/mL)	n	Inaccuracy (%Diff of mean)	Imprecision CV (%)
Pre-study	VQC.LLOQ	5.00	6	-12.40	1.85
	VQC.low	10.0	6	2.00	5.49
	VQC.mid	1000	6	8.00	1.94
	VQC.high	2000	6	8.00	0.65
In-study	QC.low	10.0	56	-4.50	7.07
	QC.mid	1000	56	6.00	4.36
	QC.high	2000	56	4.50	4.28

Pharmacokinetic Results:

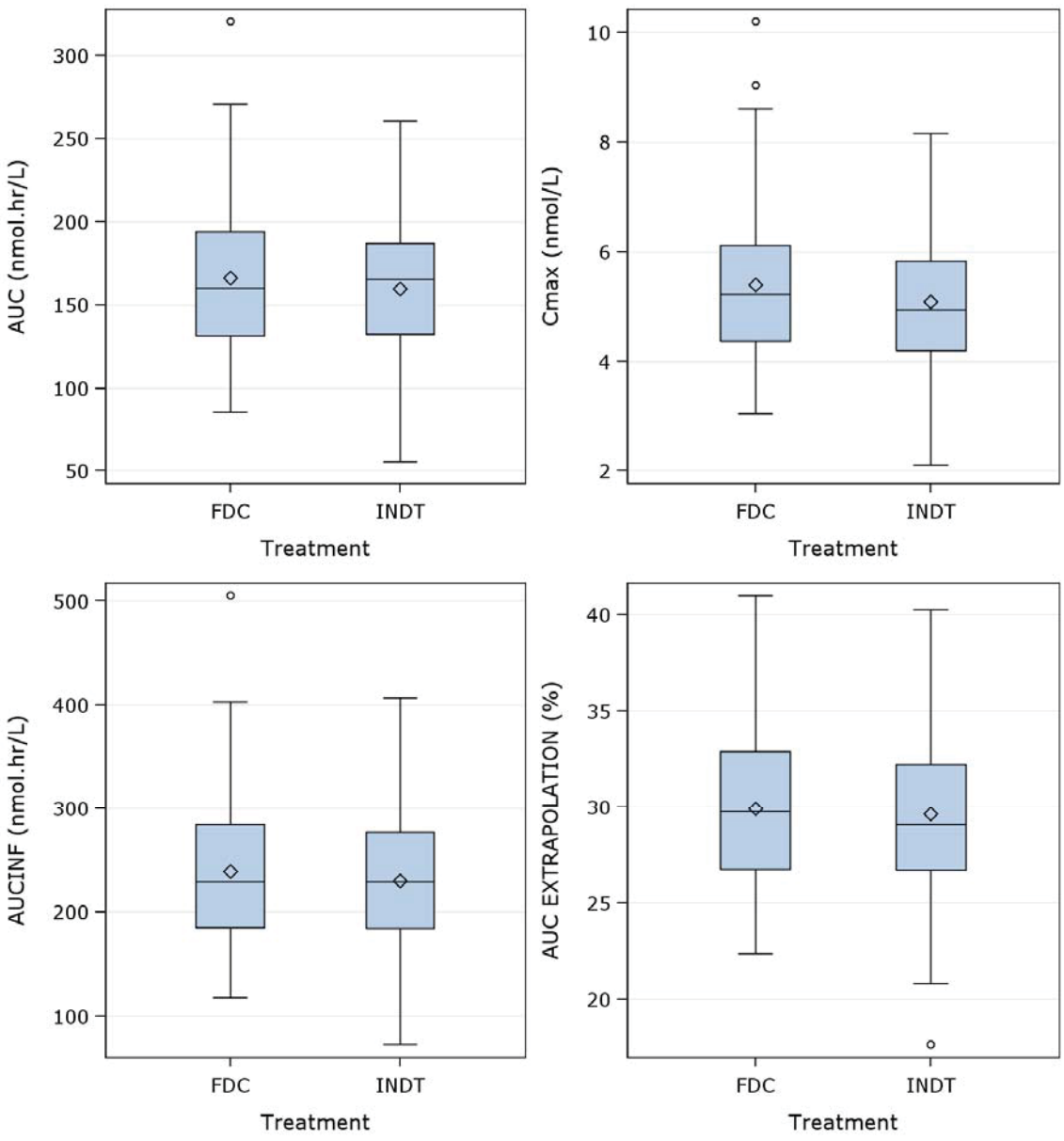
The mean concentration-time profiles of linagliptin and metformin by treatment are shown in Figure below:



Mean Concentration-time Plots by Treatment (Trial 1288.3) Lina 2.5 mg/Met 850 mg

The distribution of PK parameters by treatment for linagliptin and metformin is summarized in the figures below:

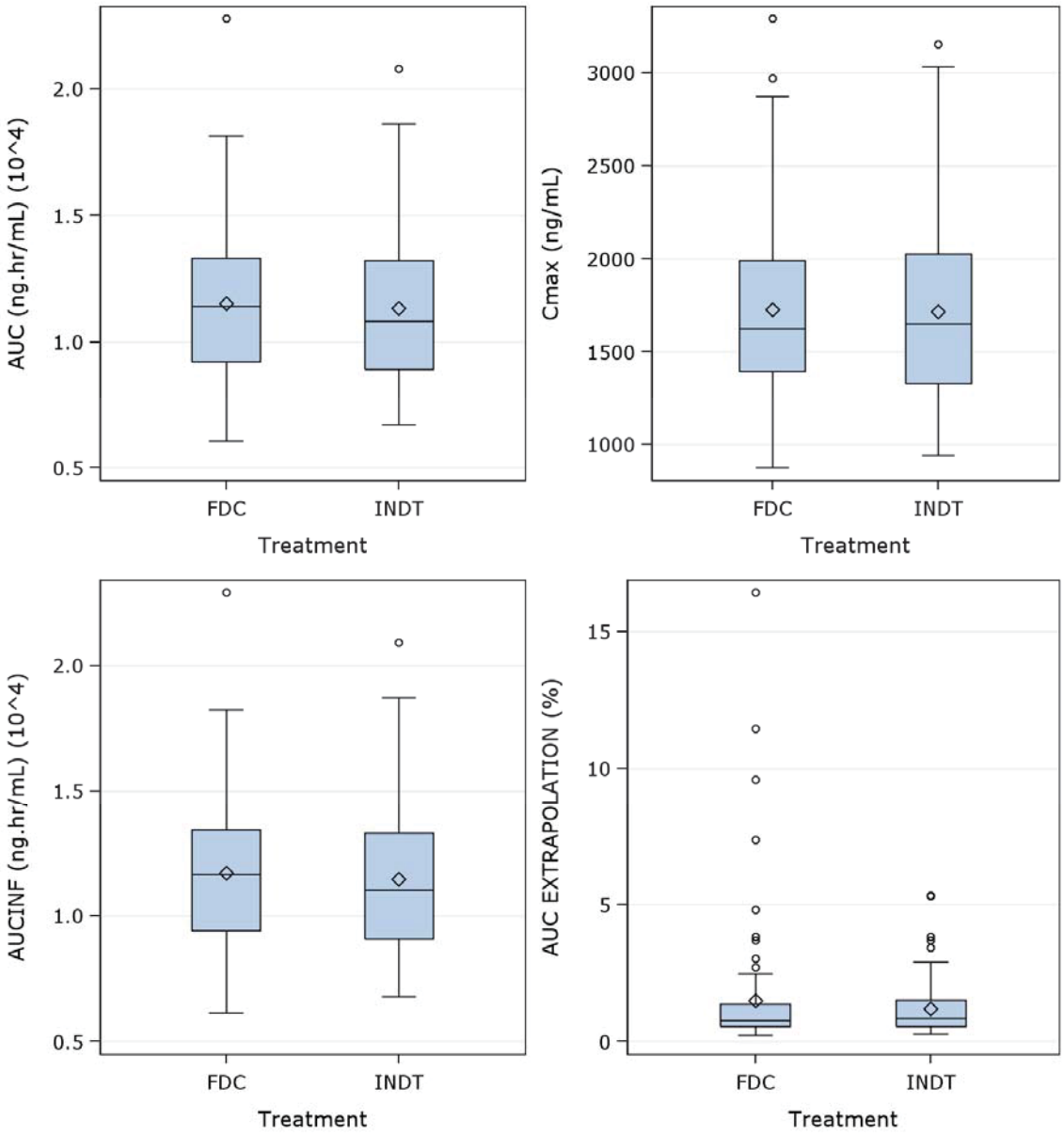
Linagliptin:



Treatment FDC= L 2.5/M 850 mg FDC Tablet (Test) INDT= Individual Tablets (Ref)

Linagliptin (BI 1356 BS) PK parameters by treatment (Trial 1288.3)

Metformin:



Treatment FDC= L 2.5/M 850 mg FDC Tablet (Test) INDT= Individual Tablets (Ref)

Metformin PK parameters by treatment (Trial 1288.3)

The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both linagliptin and metformin. Although, for linagliptin AUC0-72 h was used as primary parameter as % extrapolated is in excess of 10%.

The geometric mean ratios and 90% CIs from the statistical comparison of PK parameters are presented in the following tables.

Table 1 Statistical comparison for linagliptin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
FDC	INDT	AUC(0-inf)_Obs	nmol.hr/L	105.11	100.88 - 109.51
		AUC(0-inf)_Pred	nmol.hr/L	105.07	100.77 - 109.56
		AUC(0-t)	nmol.hr/L	104.64	100.85 - 108.57
		Cmax	nmol/L	106.35	103.12 - 109.68
		Pred_Dose_AUC	mg	101.8	91.93 - 112.74
		Pred_Dose_CMAX	mg	108.29	103.58 - 113.21
FDC = Fixed Dose Combination Tablet L/M 2.5/850 mg INDT = Individual Metformin Tablet 850 mg					

t= 72 hr for AUC0-t.

Table 2 Statistical comparison for metformin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
FDC	INDT	AUC(0-inf)_Obs	ng.hr/mL	102.18	99.07 - 105.39
		AUC(0-inf)_Pred	ng.hr/mL	102.21	99.08 - 105.43
		AUC(0-t)	ng.hr/mL	101.85	98.73 - 105.07
		Cmax	ng/mL	101.08	97.29 - 105.01
FDC = Fixed Dose Combination Tablet L/M 2.5/850 mg INDT = Individual Metformin Tablet 850 mg					

t= 72 hr for AUC0-t.

Conclusions:
The design and conduct of Trial 1288.3 are reasonable from a clinical pharmacology perspective. The protocol deviations are handled appropriately. The bioanalytical methods, as reported, adequately support the trial results. The results of the Trial 1288.3 demonstrate that the Lina 2.5/Met 850 mg FDC formulation is bioequivalent to single co-administration of Lina 2.5 mg and Glucophage® 850 mg tablets, for both linagliptin and metformin total and peak exposures.

4.2.4 BE Study (1288.4)

This study was a relative BA study to evaluate the effect of food on the pharmacokinetics of linagliptin and metformin from the intended commercial FDC formulation containing 2.5 mg linagliptin and 1000 mg metformin in a film coated, immediate release tablet.

The study design is as follows:

Title:	Relative bioavailability of a 2.5 mg lingagliptin+1000 mg metformin fixed dose combination tablet administered with and without food to healthy male and female subjects in an open, randomized, single-dose, two-way crossover Phase 1 trial
Objectives:	**Primary:** To investigate the effect of food on the relative bioavailability of a 2.5 mg linagliptin+1000 mg metformin fixed dose combination (FDC) tablet.
Study Design	Study was conducted as an open-label, randomized, single-dose, 2-way crossover design. The 2 study treatments (A and B) were as follows: A = One Linagliptin 2.5 mg/Metformin 1000 mg FDC Tablet, Oral with 240 mL of water after a high-fat, high caloric meal (Test) B = One Linagliptin 2.5 mg/Metformin 1000 mg FDC Tablet, Oral with 240 mL of water after an overnight fast of at least 10 h (Reference) The 2 treatments were separated by a washout period of at least 35 days.
Study Population	N= 32 Healthy subjects, Gender: 16 M and 16 F, Age: 38 (18-55) yr, BMI: 25 (19-29) kg/m^2
Investigational Products:	Treatment: Test / Reference Substance: Linagliptin (BI 1356) + metformin Pharmaceutical form: Film-coated FDC tablet Unit strength: 2.5 mg+1000 mg Route of administration: Oral, fed/fasted Posology: Single-dose Batch number: 903235 Expiry date: 31 Mar 2011
Sampling: Blood	Blood samples for determination of linagliptin and metformin plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (0 hour), and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 11, 12, 24, 34, 48, and 72 hours post-dose. Linagliptin accumulation half-life (t1/2) is approximately 8-12 hr, metformin has a t1/2 of approximately 6 hr; thus, a 72-h plasma concentration versus time profiling appears to be adequate for both analytes.
Urine	none
Feces	none
PK Assessments	AUC0-72 (linagliptin), AUC0-t, AUC%extrapolated, AUC0-∞, Cmax, Tmax, Kel, t1/2

Primary endpoints:	AUC0-72 and Cmax for linagliptin; AUC0-∞ and Cmax for metformin
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	None

Protocol Deviations: There were no important protocol violations in this study and no other major deviations from the study protocol.

Subject Disposition and Data Sets Analyzed:
No. of subjects planned: 32, actual who entered: 32, analyzed: 32.

Bioanalytical Results:

Linagliptin (b) (4)**:** The calibration curve of undiluted samples was linear over the range of concentrations from 0.100 to 20.0 nmol/L for BI 1356 BS. The performance summary of analytical method during sample analysis is presented below:

Linagliptin	Label	Nominal concentration [nmol/L]	N	Inaccuracy [%]	Imprecision [RSD%]
	LoQC	0.250	30	0.8	7.1
	MeQC	1.00	31	-0.1	3.9
	HiQC	15.0	31	-2.0	3.2

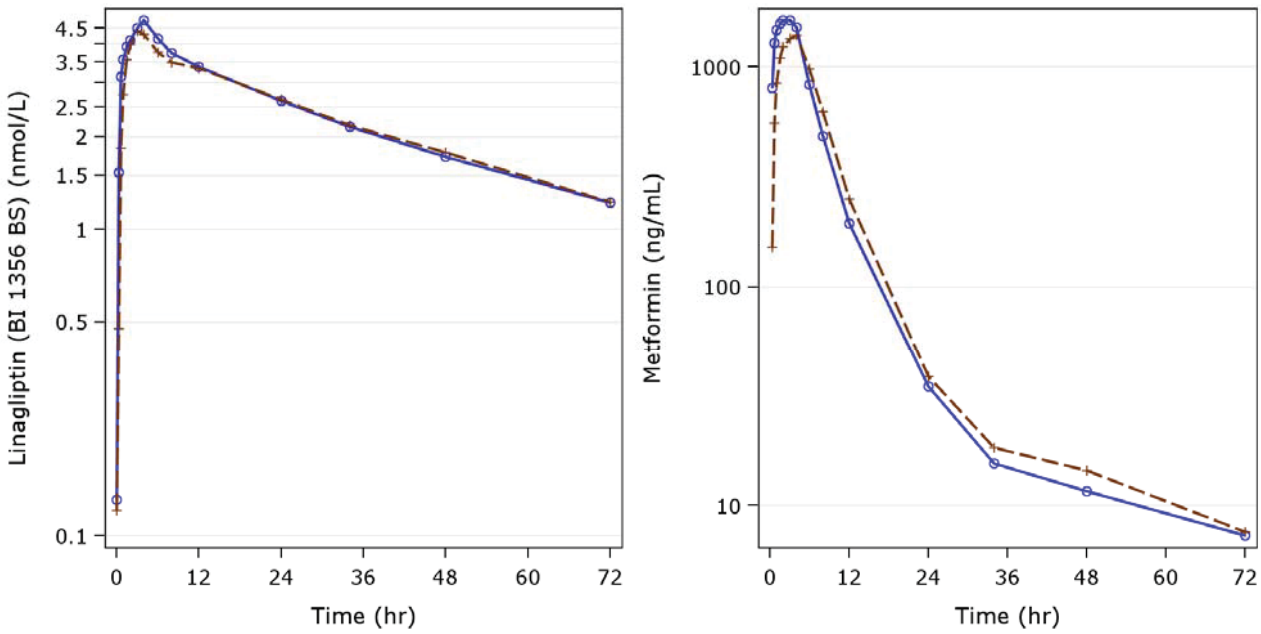
LoQC, MeQC, HiQC: low, medium or high quality control; RSD: relativ standard deviation.

Metformin (b) (4) The calibration curve of undiluted samples was linear over the range of concentrations from 5 to 2500 ng/mL for metformin. The performance summary of analytical method during sample analysis is presented below:

Metformin	Label	Concentration [ng/mL]	N	Inaccuracy [%]	Imprecision CV [%]
Pre-study	VQC.LLOQ	5.00	6	11.0	2.5
	VQC.LOW	10.0	6	2.0	3.8
	VQC.MID	200	6	1.0	1.4
	VQC.HIGH	2000	6	2.5	1.1
In-study	QC.LOW	10.0	18	4.0	4.8
	QC.MID	1000	17	0.0	4.8
	QC.HIGH	2000	18	0.5	13.1

VQC: validated quality control.

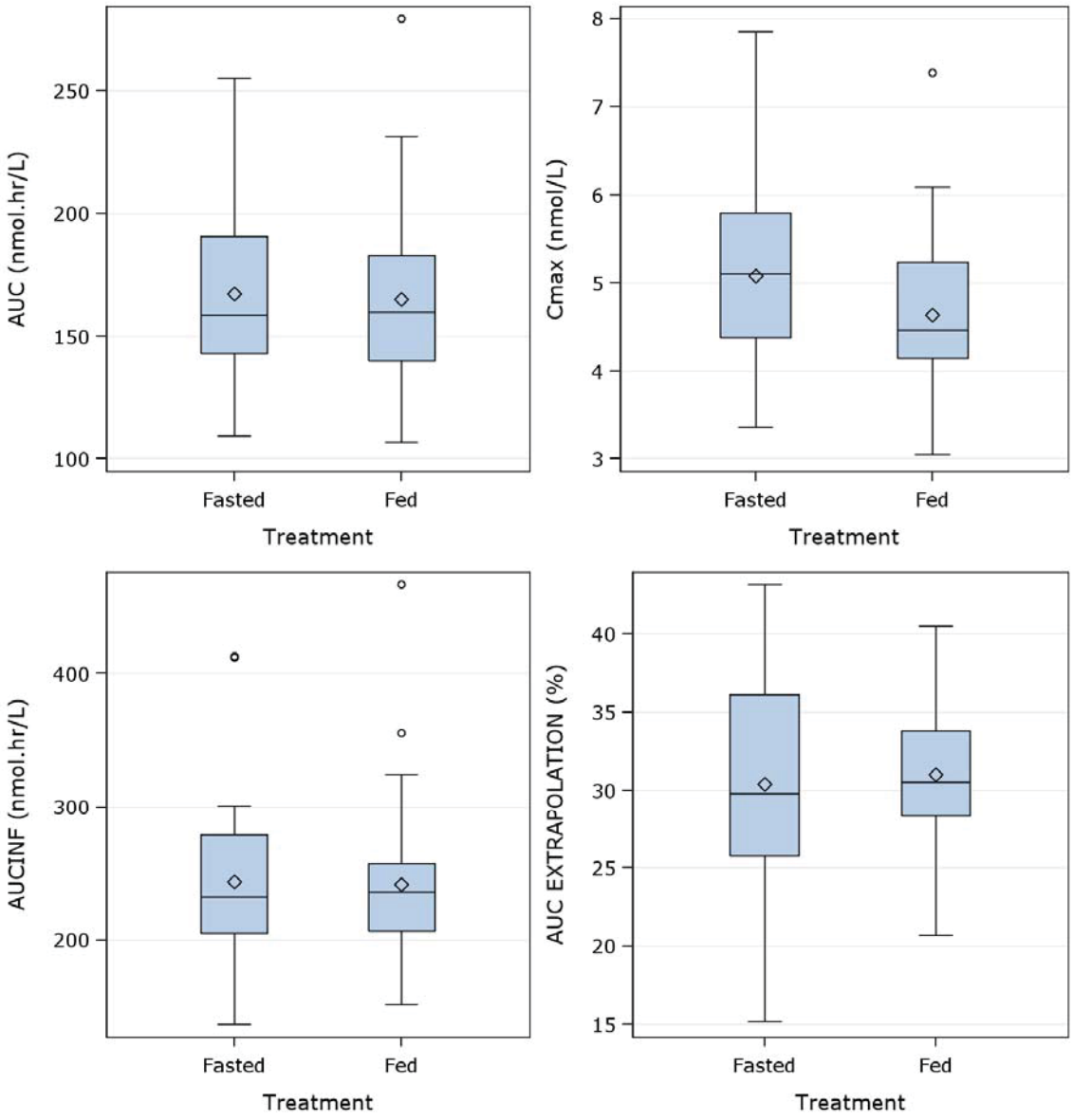
Pharmacokinetic Results:
The mean concentration-time profiles of linagliptin and metformin by treatment are shown in Figure below:



(+) Fed (Test), (O) Fasted (Ref.),
Mean(±)SE Concentration-time Plots by Treatment (Trial 1288.4) Lina 2.5 mg/Met 1000 mg Fasted versus Fed

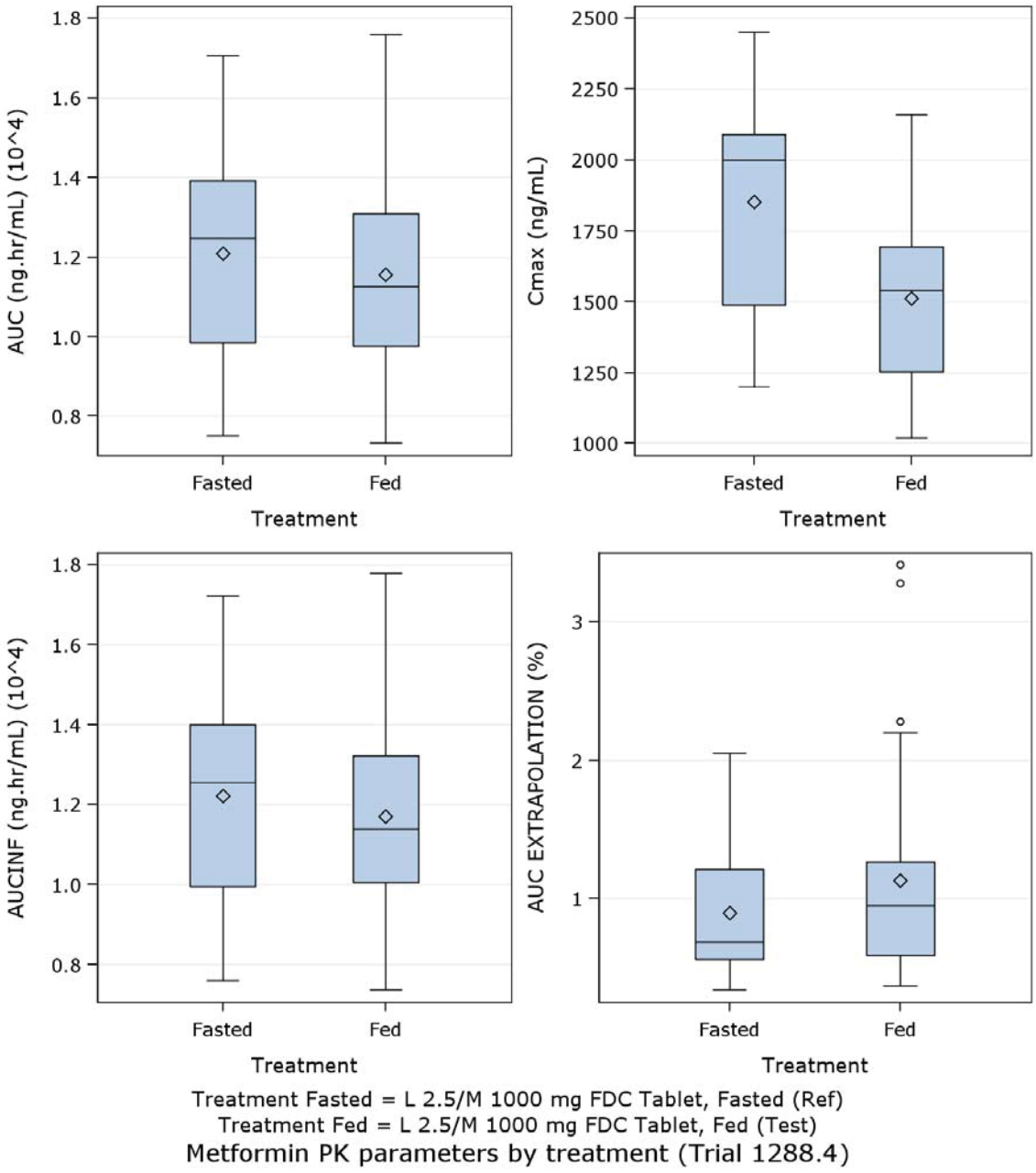
The distribution of PK parameters by treatment for linagliptin and metformin is summarized in the figures below:

Linagliptin:



Treatment Fasted = L 2.5/M 1000 mg FDC Tablet, Fasted (Ref)
Treatment Fed = L 2.5/M 1000 mg FDC Tablet, Fed (Test)
Linagliptin (BI 1356 BS) PK parameters by treatment (Trial 1288.3)

Metformin:



The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both linagliptin and metformin. Although, for linagliptin AUC0-72 h was used as primary parameter as % extrapolated is in excess of 10%.

The geometric mean ratios and 90% CIs from the statistical comparison of PK parameters are presented in the following tables.

Table 1 Statistical comparison for linagliptin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A	B	AUC(0-inf)_Obs	nmol.hr/L	99.42	94.87 - 104.18
		AUC(0-inf)_Pred	nmol.hr/L	99.98	95.24 - 104.95
		AUC(0-t)	nmol.hr/L	98.73	94.59 - 103.05
		Cmax	nmol/L	91.37	86.16 - 96.9
A = Fixed Dose Combination Tablet L/M 2.5/1000 mg, Fed B = Fixed Dose Combination Tablet L/M 2.5/1000 mg, Fasted					

t= 72 hr for AUC0-t.

Table 2 Statistical comparison for metformin PK parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A	B	AUC(0-inf)_Obs	ng.hr/mL	95.42	88.82 - 102.51
		AUC(0-inf)_Pred	ng.hr/mL	95.4	88.81 - 102.49
		AUC(0-t)	ng.hr/mL	95.2	88.52 - 102.37
		Cmax	ng/mL	81.88	76.79 - 87.31
A = Fixed Dose Combination Tablet L/M 2.5/1000 mg, Fed B = Fixed Dose Combination Tablet L/M 2.5/1000 mg, Fasted					

t= 72 hr for AUC0-t.

Conclusions:

The design and conduct of Trial 1288.4 are reasonable from a clinical pharmacology perspective. The protocol deviations are handled appropriately. The bioanalytical methods, as reported, adequately support the trial results. The results of the Trial 1288.4 demonstrate that total and peak linagliptin exposures from Lina 2.5/Met 1000 mg FDC formulation given under fed state are bioequivalent to those observed when the Lina 2.5/Met 1000 mg FDC formulation was given under fasted state. The peak exposure was ~18% lower whereas the total metformin exposure from Lina 2.5/Met 1000 mg FDC formulation given under fed state was bioequivalent to those observed when the Lina 2.5/Met 1000 mg FDC formulation was given under fasted state. A similar degree of food effect for metformin is reported for the Glucophage, however, to reduce the gastro-intestinal side effects, metformin is recommended to be taken with food. Therefore, the food effect observed in this trial is not clinically relevant.

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4.2.5 PKPD (1218.57)

This study was a BE study comparing the EU sourced 500 mg and 1000 mg metformin (Glucophage) formulations used in the Phase 3 trial 1218.46 to the corresponding US approved metformin (Glucophage).

The study design is as follows:

<table>
<tr><td>Title:</td><td>Bioequivalence of two strengths (1000 mg and 500 mg) of two different metformin tablets administered to healthy male and female subjects in an open, randomized, single dose, two-period crossover, phase I trial</td></tr>
<tr><td>Objectives:</td><td>Primary: To establish the bioequivalence of Bristol-Myers Squibb (BMS) Glucophage® tablets (US approved) and Merck Glucophage® tablets (EU) in the strengths of 1000 mg and 500 mg..</td></tr>
<tr><td>Study Design</td><td>Study was conducted as an open-label, randomized, single dose, two-period crossover design within each of the 2 study parts. The subjects of study part I received the 1000 mg Glucophage® dose whereas the subjects of study part II received the 500 mg Glucophage® dose. In each study part the subjects received 2 single doses (one Merck Glucophage® tablet as test treatment and one BMS Glucophage® tablet as reference treatment) in randomized order. If a subject received a Merck Glucophage® tablet in the first period, the BMS Glucophage® tablet was administered in the second period and vice versa.

<table>
<tr><td colspan="2">Study part I (28 subjects)</td></tr>
<tr><td>Test treatment</td><td>Reference treatment</td></tr>
<tr><td>Treatment T_1: Merck Glucophage® tablets 1000 mg</td><td>Treatment R_1: BMS Glucophage® tablets 1000 mg</td></tr>
</table>
<table>
<tr><td colspan="2">Study part II (28 subjects)</td></tr>
<tr><td>Test treatment</td><td>Reference treatment</td></tr>
<tr><td>Treatment T_2: Merck Glucophage® tablets 500 mg</td><td>Treatment R_2: BMS Glucophage® tablets 500 mg</td></tr>
</table>

Following a fast of at least 10 hours, subjects received a single oral dose of study drug on Day 1 of each treatment period. The 2 treatment periods were separated by a washout period of at least 6 days.</td></tr>
</table>

Study Population	

Parameter	Study part I (1000 mg Glucophage®)	Study part II (500 mg Glucophage®)	Total
Number of subjects [N (%)]	28 (100.0)	28 (100.0)	56 (100.0)
Age [years]			
Mean (SD)	36.0 (10.2)	37.2 (9.9)	36.6 (10.0)
Gender [N (%)]			
Male	15 (53.6)	13 (46.4)	28 (50.0)
Female	13 (46.4)	15 (53.6)	28 (50.0)
Height [cm]			
Mean (SD)	175.8 (8.8)	172.1 (8.6)	173.9 (8.8)
Weight [kg]			
Mean (SD)	68.4 (12.7)	73.5 (13.6)	71.0 (13.3)
Body mass index [kg/m^2]			
Mean (SD)	22.94 (2.8)	23.63 (2.6)	23.29 (2.7)
Smoking status [N (%)]			
Never smoked	13 (46.4)	14 (50.0)	27 (48.2)
Ex-smoker	10 (35.7)	9 (32.1)	19 (33.9)
Currently smokes	5 (17.9)	5 (17.9)	10 (17.9)
Alcohol status [N (%)]			
Non drinker	5 (17.9)	9 (32.1)	14 (25.0)
Drinks - no interference*	23 (82.1)	19 (67.9)	42 (75.0)
Drinks - possible interference**	0 (0.0)	0 (0.0)	0 (0.0)

* no interference with trial participation, **possible interference with trial participation

Investigational Products:	The characteristics of the test product (T) are given below. Substance: metformin hydrochloride (Glucophage®) Pharmaceutical form: film-coated tablet Batch no.: 250086 (500 mg) and 200846 (1000 mg) Expiry dates: November 2010 (1000 mg) and 30 June 2012 (500 mg) Source: European commercial market Producer: Merck Pharma GmbH, Darmstadt, Germany Strengths: 1000 mg and 500 mg Daily dose: 1000 mg or 500 mg Duration of use: single dose Route of administration: oral The characteristics of the reference product (R) are given below. Substance: metformin hydrochloride (Glucophage®) Pharmaceutical form: film-coated tablet Batch no.: 7K28757A (500 mg) and 8D2508A (1000 mg) Expiry dates: 30 April 2011 (1000 mg) and 31 October 2011 (500 mg) Source: US commercial market Producer: Bristol-Myers Squibb Company, Princeton, New Jersey, USA Strengths: 1000 mg and 500 mg Daily dose: 1000 mg or 500 mg Duration of use: single dose Route of administration: oral
Sampling: Blood	Blood samples for determination of metformin plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (0 hour), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, and 48 hours post-dose. Metformin has a t1/2 of approximately 6 hr; thus, a 48-h plasma concentration versus time profiling appears to be adequate.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞, Cmax, Tmax, Kel, t1/2, CL/F, V/F
Primary PK endpoints:	AUC0-∞ and Cmax for metformin

Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	None

Protocol Deviations: No important protocol deviations and no violations of inclusion or exclusion criteria occurred in this study.

Subject Disposition and Data Sets Analyzed:
No. of subjects planned: 56
Actual who entered: 56
Study Part I: Allocated: 28, Completed: 28.
Study Part II: Allocated: 28, Completed: 28.
Two analysis sets were defined for this study. The treated set consisted of all subjects who received at least one dose of study medication. Both the safety evaluation and the primary PK analysis were performed on the treated set. Sensitivity analyses were performed on the pharmacokinetic per-protocol set (PK-PPS), which was defined as all subjects in the treated set who:

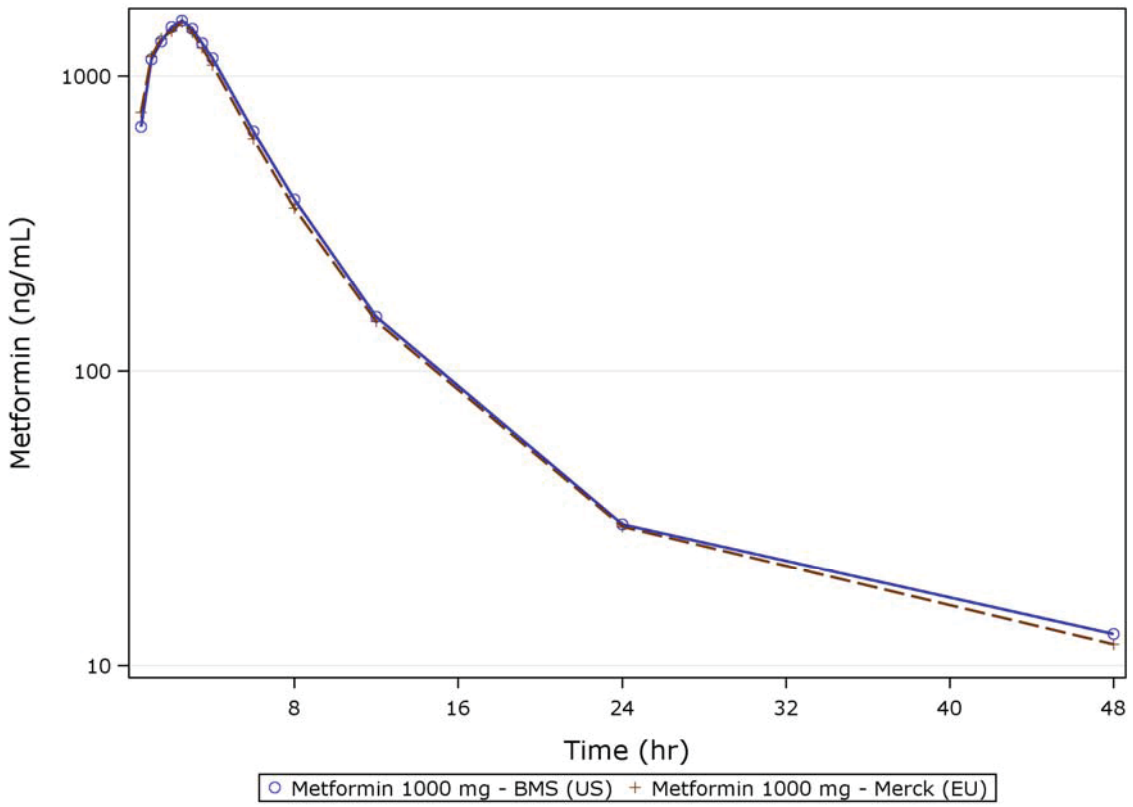
- Did not experience vomiting within twice median tmax (i.e. within 5 h)
- Completed the trial according to the trial protocol without important protocol violations relevant to the evaluation of bioequivalence

All 56 randomised subjects were included in the treated set, and 55 subjects were included in the PK-PPS. Subject No. 208 was excluded from the PK-PPS as the subject vomited 3 min after intake of 500 mg Glucophage® from Merck (study part II). For the period in which the vomiting occurred, the values of the pharmacokinetic endpoints were excluded. Subjects with diarrhoea or loose stool within twice median tmax were included in the PK-PPS as diarrhea and loose stool most likely do not affect drug absorption of an immediate release formulation (like Glucophage®).

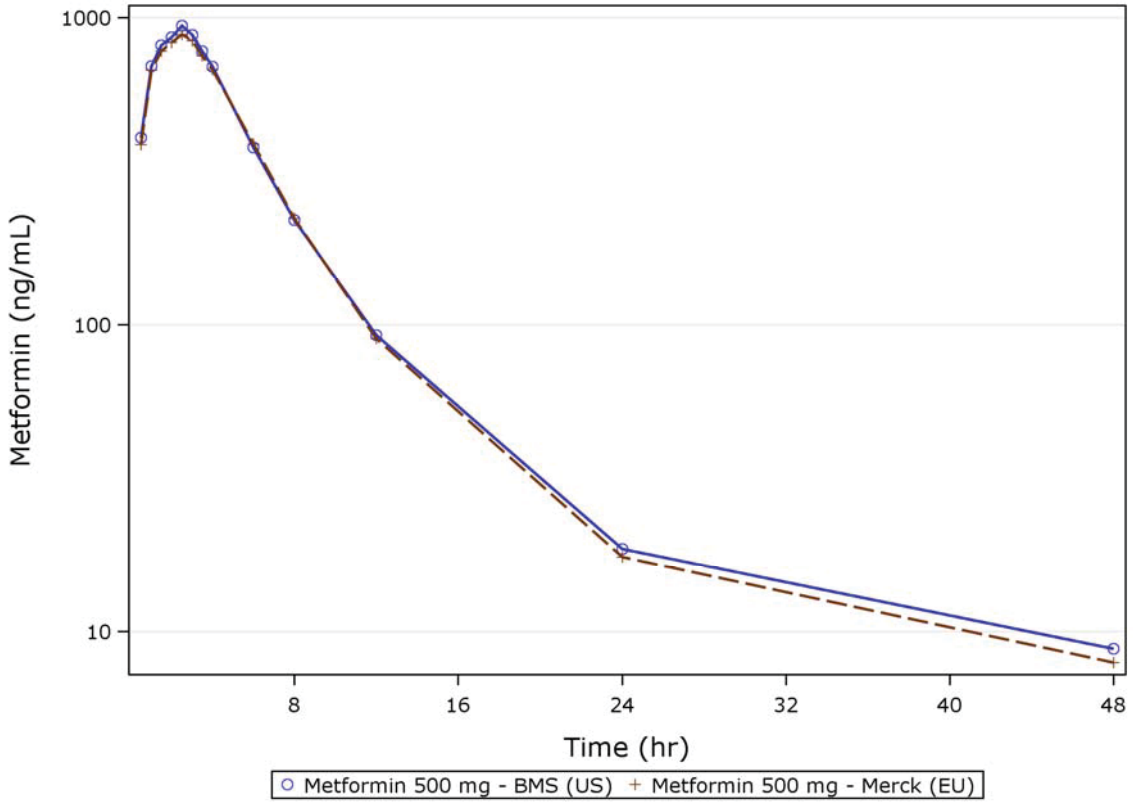
Bioanalytical Results:
Metformin (b) (4) The calibration curve of undiluted samples was linear over the range of concentrations from 5 to 2500 ng/mL for metformin. The performance summary of analytical method during sample analysis is presented below:

Metformin	Label	Concentration [ng/mL]	N	Deviation (%)	Coefficient of variation (%)
In-study	QC.1	10	32	6.00	6.55
	QC.2	200	31	2.50	3.74
	QC.3	2000	32	5.00	4.28

Pharmacokinetic Results:
The mean concentration-time profiles of metformin 1000 mg (Part I) and 500 mg (Part II) formulations by treatment are shown in Figures below:



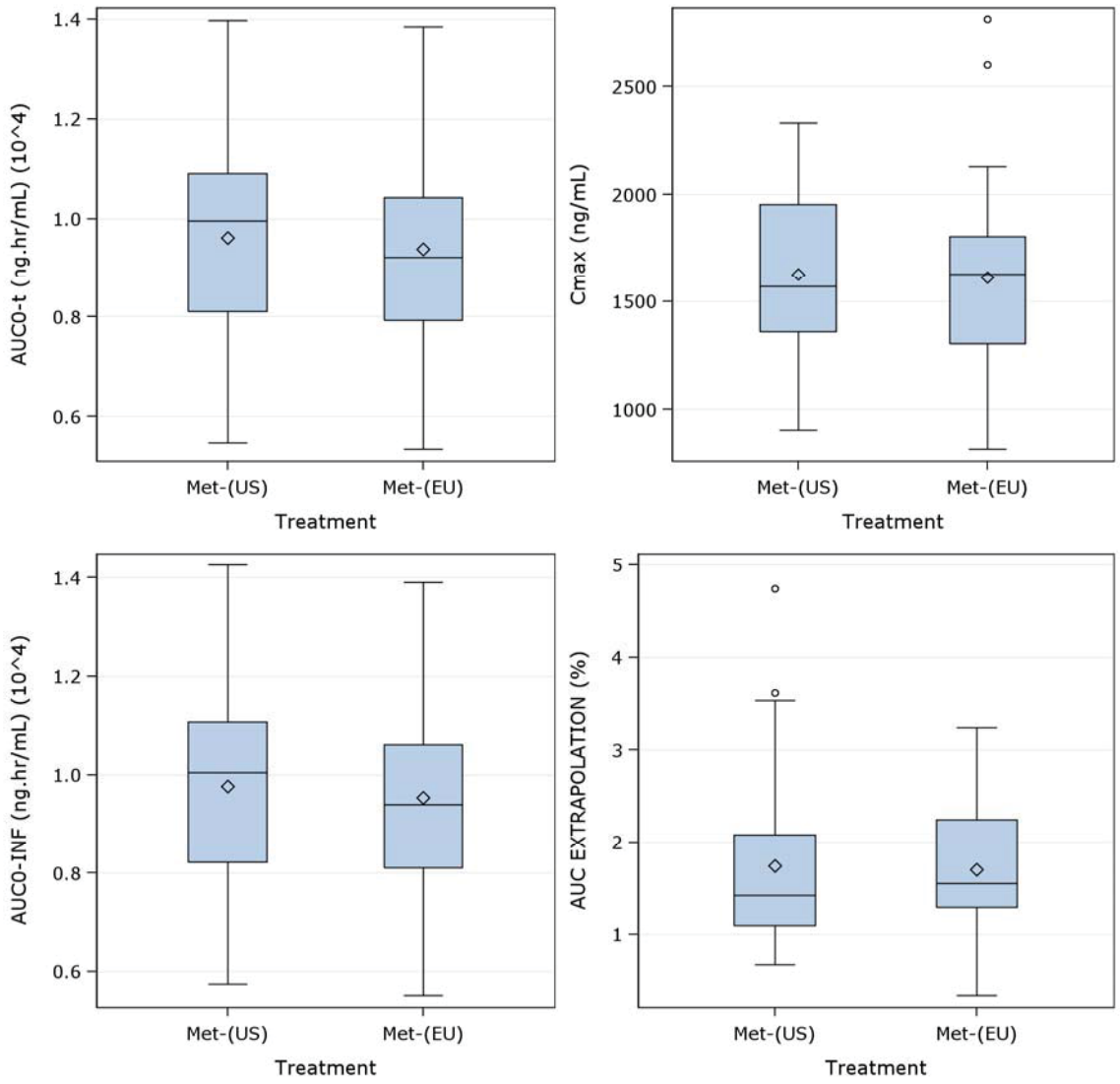
Mean(±)SE Concentration-time Plots by Treatment (Trial 1218.57 - Part I)



Mean(±)SE Concentration-time Plots by Treatment (Trial 1218.57 - Part II)

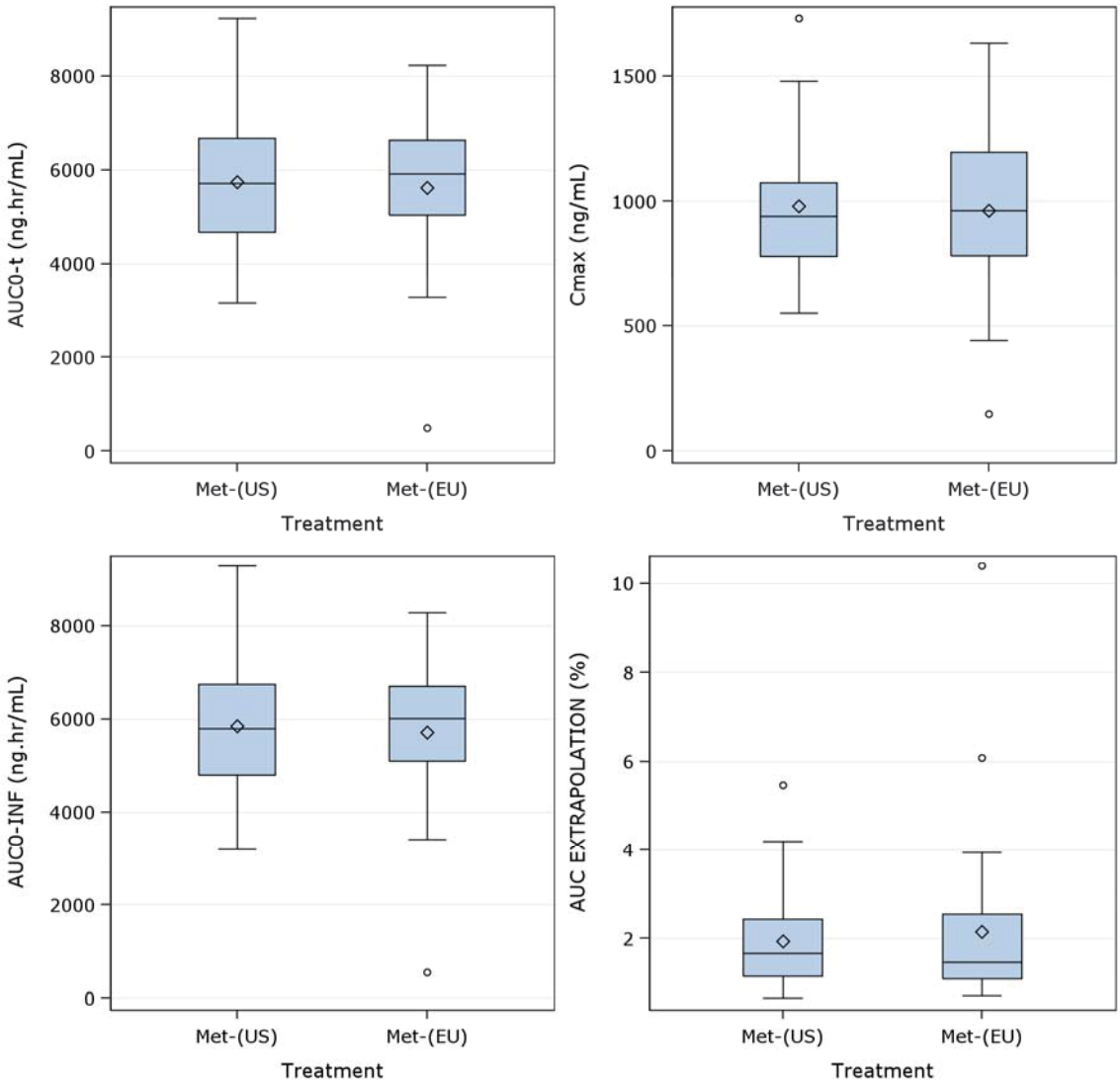
The distribution of PK parameters by treatment for metformin is summarized in the figures below:

Metformin 1000 mg (Part I):



Metformin PK parameters by treatment for 1000 mg formulations (Trial 1218.57-Part I)

Metformin 500 mg (Part II):



Metformin PK parameters by treatment for 500 mg formulations (Trial 1218.57-Part II)

The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both linagliptin and metformin.

The geometric mean ratios and 90% CIs from the statistical comparison of PK parameters are presented in the following tables.

Table 1 Statistical comparison for metformin PK parameters for 1000 mg (Part I)

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A	B	AUC(0-inf)_Obs	ng.hr/mL	97.56	91.83 - 103.66
		AUC(0-inf)_Pred	ng.hr/mL	97.64	91.89 - 103.75
		AUC(0-t)	ng.hr/mL	97.6	91.76 - 103.82
		Cmax	ng/mL	98.39	90.8 - 106.61
A = Metformin 1000 mg Tablet Merck (EU) B = Metformin 1000 mg Tablet BMS (US)					

t= 72 hr for AUC0-t.

Table 2 Statistical comparison for metformin PK parameters for 500 mg (Part I)

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A	B	AUC(0-inf)_Obs	ng.hr/mL	102.42	95.78 - 109.52
		AUC(0-inf)_Pred	ng.hr/mL	102.37	95.67 - 109.54
		AUC(0-t)	ng.hr/mL	102.52	95.56 - 110
		Cmax	ng/mL	102.26	92.06 - 113.6
A = Metformin 500 mg Tablet Merck (EU) B = Metformin 500 mg Tablet BMS (US)					

t= 72 hr for AUC0-t.

Conclusions:
The design and conduct of Trial 1218.57 are reasonable from a clinical pharmacology perspective. The protocol deviations are handled appropriately. The bioanalytical methods, as reported, adequately support the trial results. The results of the Trial 1218.57 demonstrate that both 1000 mg and 500 mg metformin tablets from EU source Glucophage® (Merck, Germany) are bioequivalent to their respective reference US approved Glucophage® tablets (BMS, US), for total and peak metformin exposures.

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4.2.6 PKPD Study (1218.45)

This study was a PKPD study comparing the PKPD profile from multiple 5 mg doses of linagliptin (BI 1356) p.o. given once daily compared to multiple 2.5 mg doses given twice daily.

The study design is as follows:

<table>
<tr><td>Title:</td><td>Pharmacokinetics and pharmacodynamics of multiple 5 mg doses of BI 1356 p.o. given once daily compared to multiple 2.5 mg doses given twice daily in healthy male and female volunteers. A monocentric, open-label, crossover trial</td></tr>
<tr><td>Objectives:</td><td>Primary: The objective was to investigate the influence of 2 different dosage regimens (5 mg once daily vs. 2.5 mg twice daily) on the steady-state pharmacokinetics and pharmacodynamics of orally administered BI 1356.</td></tr>
<tr><td>Study Design</td><td>The study was conducted according to an open-label, multiple-dose, two-way crossover designs. The duration of each of the 2 treatment periods was 7 days. The treatment periods were not separated by a wash-out period.</td></tr>
<tr><td colspan="2">
<table>
<tr><td>Visit 1</td><td colspan="2">Visit 2</td><td colspan="2">Visit 3</td><td>Visit 4</td></tr>
<tr><td>Days -21 to 1</td><td>Day 1 to 6</td><td>Day 7</td><td>Days 8 to 13</td><td>Day 14</td><td>Days 22 to 26</td></tr>
<tr><td></td><td colspan="2">AB: 5 mg BI 1356 q.d.
BA: 2.5 mg BI 1356 b.i.d.</td><td colspan="2">AB: 2.5 mg BI 1356 b.i.d.
BA: 5 mg BI 1356 q.d.</td><td></td></tr>
<tr><td></td><td>PK/PD[1]</td><td>PK/PD</td><td>PK/PD[2]</td><td>PK/PD</td><td></td></tr>
<tr><td>screening</td><td>ambulatory</td><td>in-house</td><td>ambulatory</td><td>in-house</td><td>e.o.s.</td></tr>
</table>
q.d.=once daily, b.i.d.=twice daily, e.o.s.=end-of-study examination, PK=pharmcokinetics, PD=pharmacodynamics
[1] at trough, Days 5 and 6
[2] at trough, Days 12 and 13
</td></tr>
<tr><td>Study Population</td><td>N= 16 Healthy subjects, Gender: 42 M and 54 F, Age: 37 (19-55) yr, BMI: 24 (19-29) kg/m^2</td></tr>
<tr><td>Investigational Products:</td><td>
<table>
<tr><td></td><td>Treatment A</td><td>Treatment B</td></tr>
<tr><td>Substance</td><td>BI 1356</td><td>BI 1356</td></tr>
<tr><td>Pharmaceutical form</td><td>film-coated tablet</td><td>film-coated tablet</td></tr>
<tr><td>Source</td><td>Boehringer Ingelheim Pharma GmbH & Co. KG</td><td>Boehringer Ingelheim Pharma GmbH & Co. KG</td></tr>
<tr><td>Batch number</td><td>B071001960</td><td>B071001873</td></tr>
<tr><td>Unit strength</td><td>5 mg</td><td>2.5 mg</td></tr>
<tr><td>Posology</td><td>1-0-0</td><td>1-0-1</td></tr>
<tr><td>Route of administration</td><td>oral</td><td>oral</td></tr>
<tr><td>Duration of use</td><td>7 days</td><td>7 days</td></tr>
</table>
</td></tr>
<tr><td>Sampling: Blood</td><td>Blood samples for determination of linagliptin and metformin plasma concentrations were measured at the following times on Day 7 for each treatment period:</td></tr>
</table>

	QD Regimen: 50 minutes pre-dose (0 hour), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 11, 12, 16, ~24 hours post-dose on either Day 7 (Seq AB) or Day 14 (Seq BA). BID Regimen: 50 minutes pre-dose (0 hour), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 11.75 after first, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post second dose on either Day 7 (Seq BA) or Day 14 (Seq AB).
Urine	Yes
Feces	none
PK Assessments	Primary PK parameter: AUC0-24,ss Secondary PK parameters: Cmax,ss, Cpre,N, tmax,ss, AUC0-12,ss, CL/F,ss, CLR,ss, and urinary excretion parameters: Aet1-t2,ss, fet1-t2,ss
PD Assessments:	Pharmacodynamic parameters for dipeptidyl-peptidase 4 (DPP-4) inhibition at steady-state: Eavg0-24,ss, Eavg0-12,ss, E24,ss, E12,ss, Emax,ss, Emin,ss
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs

Protocol Deviations: Due to the change to daylight-saving time in the early morning of 30 Mar 2008 (approximately 18 h after the first dose of the 2.5 mg twice daily regimen and 42 h after the first dose of the 5 mg once daily regimen, respectively), lots of deviations of about 60 min from planned times were recorded for vital signs recording times, laboratory blood sampling times, and PK/PD blood and urine sampling times. After the change to daylight-saving time, the assessments were performed at the same clock times as before, so that the time differences were actually -1 h. No important protocol deviations were reported in the trial. All 16 subjects were included in the analysis of safety, whereas 15 subjects were included in the PK/PD analysis. No PK data are available for Subject No. 11, who discontinued due to an AE (influenza-like illness) on Day 5 of the first treatment period and was completely excluded from the PK set. This refers to both treatment periods.

Subject Disposition and Data Sets Analyzed:
No. of subjects planned: 16
Actual who entered: 16
Treatment A (FDC tablet): Treated: 16, analyzed (for primary endpoints): 15
Treatment B (single tablets): Treated: 96, analyzed (for primary endpoints): 94 (L)/93(M).

Bioanalytical Results:

Linagliptin (b) (4)***:*** The calibration curve of undiluted samples was linear over the range of concentrations from 0.1 to 100 nmol/L for BI 1356 BS. The performance summary of analytical method during sample analysis is presented below:

BI 1356	Label	Concentration [nmol/L]	N	Inaccuracy [%]	Imprecision [%]
in-study	LoQC	0.25	22	-0.4	9.0
	LoQC1	1.0	22	-2.7	6.1
	MeQC	5.0	22	-1.6	5.5
	HiQC	80	22	-8.9	3.6

Linagliptin Measurement in Urine: The calibration standards ranged from 1 to 1000 nmol/L for BI 1356 BS in undiluted samples using 40 µL of urine.

BI 1356	Label	Nominal concentration [nmol/L]	N	Inaccuracy [%]	Imprecision [%]
	LoQC	2.5	6	4	6.3
	MeQC	50	6	8.4	3.1
	HiQC	800	6	-1.1	3.5

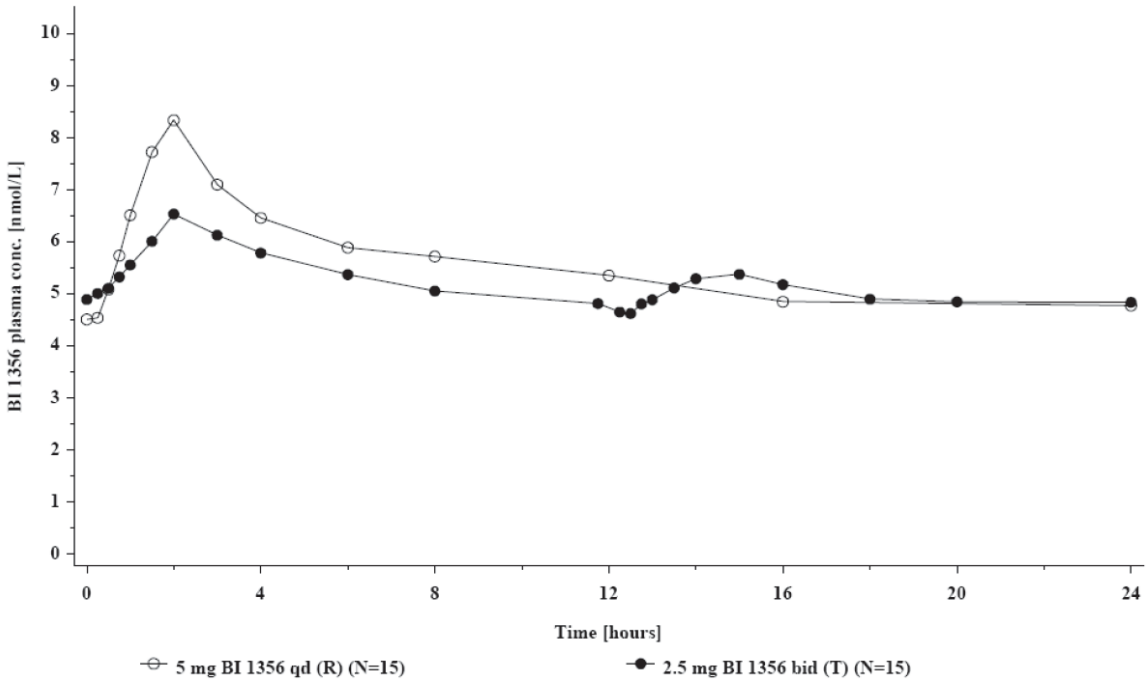
DPP4 Activity Measurement: A total of 648 human EDTA plasma samples were analyzed for DPP-4 activity using a validated semi-quantitative enzyme activity assay with fluorescence detection at the [redacted] (b) (4) The performance summary of analytical method during sample analysis is presented below:

	DPP-4 activity [%] CV [%]	DPP-4 activity [RFU] CV [%]
Imprecision at DPP-4 K1	1.56	2.76
Imprecision at DPP-4 K2	1.56	2.59
Imprecision at DPP-4 K3	1.81	3.97
Imprecision at DPP-4 K4	1.88	2.75
Imprecision at DPP-4 K5	0.97	2.64
Imprecision at DPP-4 K6	Not applicable	3.21

Pharmacokinetic Results:

Geometric mean drug plasma concentration-time profiles after multiple oral administration of 5 mg BI 1356 once daily for 7 days and multiple oral administration of 2.5 mg BI 1356 twice daily for 7 days are shown in Figure below:

Day 7



The comparison of PK parameters by treatment for linagliptin are summarized in the table below:

		5 mg q.d. BI 1356 (R)		2.5 mg b.i.d. BI 1356 (T)	
		gMean (N=15)	gCV [%]	gMean (N=15)	gCV [%]
$AUC_{0-24,ss}$	[nmol·h/L]	132	18.0	124	14.2
$CL/F_{,ss}$[1]	[mL/min]	1330	18.0	1420	14.2

[1] $CL/F_{,ss}$ for the b.i.d. treatment was calculated over a 24-h interval.

Summary of PK Parameters for 5 mg QD:

		5 mg q.d. BI 1356	
		gMean (N=15)	gCV [%]
$AUC_{0-12,ss}$	[nmol·h/L]	73.6	18.4
$C_{max,ss}$	[nmol/L]	9.02	24.9
$t_{max,ss}$[1]	[h]	1.50	0.750-2.03
$CL/F_{,ss}$	[mL/min]	1330	18.0
$fe_{0-12,ss}$	[%]	2.14[2]	36.9[2]
$fe_{0-24,ss}$	[%]	3.17[2]	34.0[2]
$CL_{R,0-12,ss}$	[mL/min]	50.9[2]	20.6[2]
$CL_{R,0-24,ss}$	[mL/min]	42.1[2]	19.8[2]

[1] For t_{max} median and range (min-max) are given.
[2] N=14 (see explanation given in the text).

Comparison of pharmacokinetic parameters of 2.5 mg BI 1356 twice daily by dose:

		2.5 mg b.i.d. BI 1356 dose 13 – morning administration		2.5 mg b.i.d. BI 1356 dose 14 – evening administration	
		gMean (N=15)	gCV [%]	gMean (N=15)	gCV [%]
$AUC_{0-12,ss}$	[nmol·h/L]	64.8	14.3	59.6	14.3
$C_{max,ss}$	[nmol/L]	6.88	14.2	5.70	15.5
$t_{max,ss}$[1]	[h]	2.00	0.750-4.00	2.07	1.00-11.4
$CL/F_{,ss}$	[mL/min]	1360	14.3	1480	14.3
$fe_{0-12,ss}$	[%]	3.06	37.0	2.23	31.9
$CL_{R,0-12,ss}$	[mL/min]	41.7	33.4	33.0	30.5

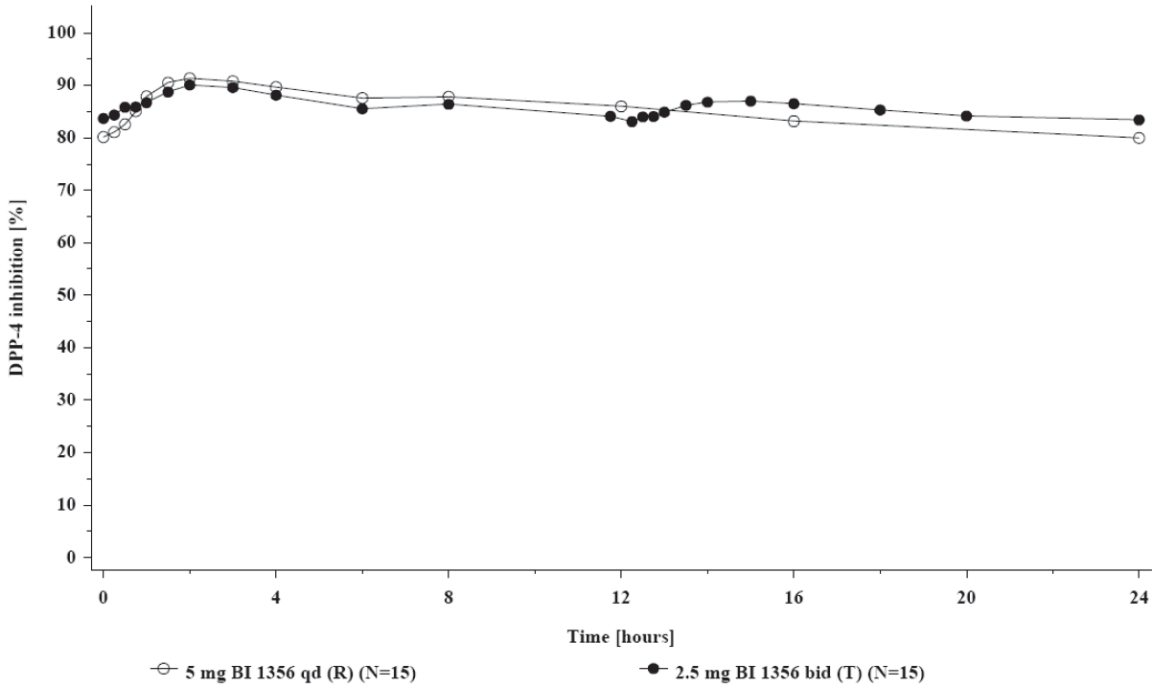
[1] For t_{max} median and range (min-max) are given.

The geometric mean ratios and 90% CIs from the statistical comparison of PK parameters are presented in the following tables.

Table 1 Statistical comparison for linagliptin PK parameters

Parameter	N	Test	Reference	Intra-individual gCV [%]	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90% confidence interval	
						Lower limit [%]	Upper limit [%]
$AUC_{0\text{-}24,ss}$ [nmol·h/L]	15	2.5 mg b.i.d. BI 1356	5 mg q.d. BI 1356	7.4	93.89	89.49	98.51

Pharmacodynamic Results:



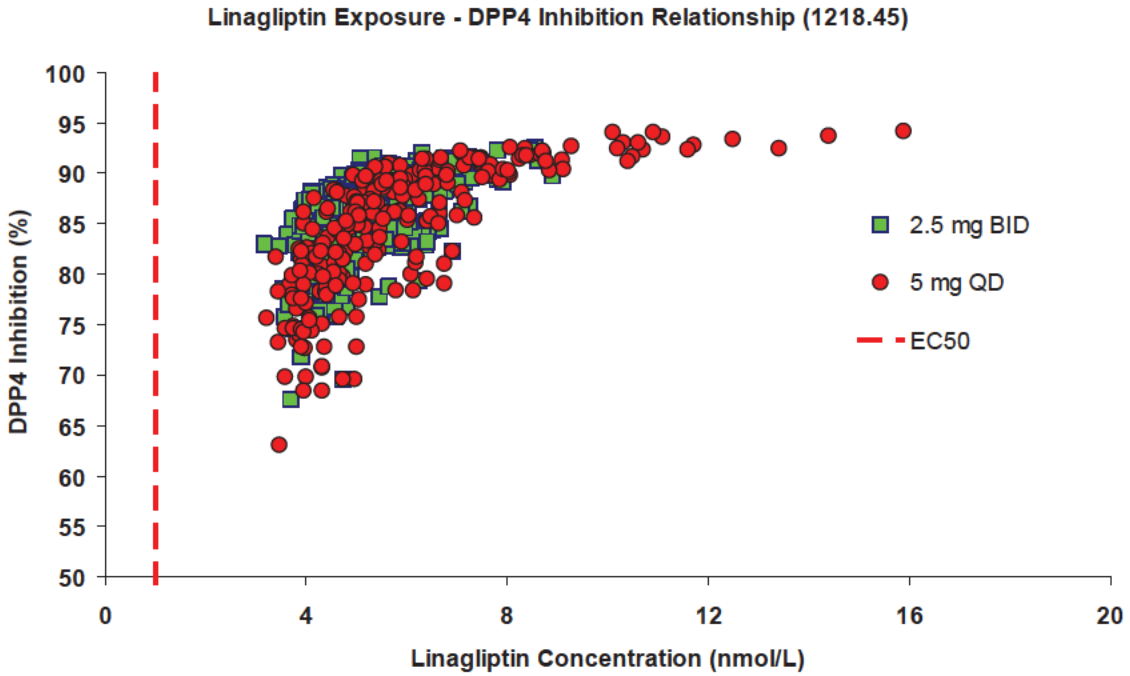
Comparison of pharmacodynamic parameters of DPP-4 inhibition by treatment:

DPP-4 Inhibition		5 mg q.d. BI 1356 (R)		2.5 mg b.i.d. BI 1356 (T) dose 13 – morning administration		2.5 mg b.i.d. BI 1356 (T) dose 14 – evening administration	
		Mean (N=15)	CV [%]	Mean (N=15)	CV [%]	Mean (N=15)	CV [%]
$E_{max,ss}$	[%]	92.1	1.41	90.6	1.38	88.3	1.81
$E_{avg0\text{-}12,ss}$	[%]	NC	NC	86.6	2.59	85.0	2.80
$E_{avg0\text{-}24,ss}$[1]	[%]	85.3	3.79	85.8	2.65	see dose 13	see dose 13
$E_{12,ss}$	[%]	NC	NC	84.1	3.61	83.4	3.47
$E_{24,ss}$	[%]	80.0	6.76	NC	NC	NC	NC

[1] $E_{avg0\text{-}24,ss}$ for b.i.d. treatment was calculated as sum of $E_{avg0\text{-}12,ss}$ after dose 13 and dose 14.

The average DPP-4 inhibition over a 24-h interval at steady-state (Eavg0-24,ss) was similar for both dosage regimens (5 mg once daily: 85.3%; 2.5 mg twice daily: 85.8%). The interindividual variability in average DPP-4 inhibition over 24 h was low, ranging from 2.65 to 3.79% CV.

PKPD:



Conclusions:

The design and conduct of Trial 1288.3 are reasonable from a clinical pharmacology perspective. The protocol deviations are handled appropriately. The bioanalytical methods, as reported, adequately support the trial results. The results of the Trial 1288.3 demonstrate that:

- The 2.5 mg BI 1356 twice daily regimen and the 5 mg BI 1356 once daily regimen resulted in a comparable 24-h exposure. However, the claim for bioequivalence based on $AUC_{24h,ss}$ is not reasonable considering that Cmax with 2.5 mg BID was lower than that observed for 5 mg QD.
- Both dosage regimens resulted in a DPP-4 inhibition greater or equal than 80% at trough. DPP-4 inhibition was comparable for both dosage regimens over the whole 24-h interval at steady-state. The average DPP-4 inhibition was 85.3% for the 5 mg once daily regimen and 85.8% for the 2.5 mg twice daily regimen..

4.3 OCP Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	201281	Brand Name	Linagliptin/Metformin FDC
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Linagliptin, Metformin hydrochloride
Medical Division	DMEP	Drug Class	Anti-diabetic (Type 2 Diabetes)
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	Indicated for the treatment of Type 2 Diabetes Mellitus.
		Dosage Form	Film-coated Tablets 2.5 mg Linagliptin(L) / 500 mg Metformin (M), 2.5 mg L / 850 mg M, and 2.5 mg L / 1000 mg M film-coated, IR, (b) (4) tablets
OCP Team Leader	Sally Choe, Ph.D.	Dosing Regimen	One tablet twice daily
Date of Submission	January 19, 2011	Route of Administration	Oral
Estimated Due Date of OCP Review	September 7, 2011	Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
PDUFA Due Date	November 19, 2011	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments if any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	**X**			
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	1		**1218.4**
In-vivo effects of primary drug:	**X**			**1218.4**
In-vitro:	**X**	1		**A244/08LU**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	2		**1288.45, 1218.47**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	4		**1288.1, 1288.2, 1288.3, 1288.57**
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	1		**1288.4**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**9**		

Filability		
	"X" if yes	Comments
Is Application filable?	X	**Comments to the Sponsor:** Please provide raw concentration and PK/PD parameter data (preferably as SAS transport files) for all BE studies (1288.1, 1288.2, 1288.3, 1288.4, and 1218.57) and the PKPD study (1218.45). • The concentration data-set(s) should at least have the following columns: ID, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence. • The PK/PD parameter data set(s) should at minimum have the following columns: ID, Trial Number, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence.
Submission in Brief: See the details below.		**Reviewer's Comments to project manager:** **1. Please send a consult to DSI for inspection of the pivotal BE studies:** **1288.1:** • **Clinical Site and PI:** ○ **Principal Investigator: Dr Mario Iovino, Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre/Dept. of Clinical Research, Birkendorfer Strasse 65, Biberach, Germany** **1218.57:** • **Clinical Site and PI:** ○ **Principal Investigator: Dr Mario Iovino, Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre/Dept. of Clinical Research, Birkendorfer Strasse 65, Biberach, Germany** **Bioanalytical Sites for both studies:** (b) (4) [redacted] **2. From clinical pharmacology we have information requests for the sponsor to be sent in Day-74 letter as highlighted above.**

#Studies submitted with Analysis Data sets

Submission in Brief:

Sponsor, Boehringer Ingelheim Pharmaceuticals, Inc. has submitted a new drug application for Linagliptin /Metformin hydrochloride (hereafter LM) film-coated fixed-dose combination (FDC) tablets for the treatment of type 2 diabetes mellitus. The proposed indication for LM is "*an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with linagliptin+metformin is appropriate*". The active pharmaceutical ingredients in LM drug product are linagliptin, a dipeptidyl peptidase (DPP4) inhibitor, and metformin HCL, a widely prescribed oral antidiabetic.

LM will be available as three dosage strength immediate-release tablets:

- 2.5 mg Linagliptin / 500 mg Metformin HCL,

- 2.5 mg Linagliptin / 850 mg Metformin HCL, and
- 2.5 mg Linagliptin / 1000 mg Metformin HCL.

The proposed recommended daily dose of LM is one tablet taken twice daily.

Pharmacokinetics, safety, and efficacy profiles of linagliptin monotherapy have been evaluated in the studies reported in NDA 201280, currently under review by the agency. The clinical development program for linagliptin+metformin FDC consists of 13 clinical studies: six Phase I studies (one of these, 1218.4, was conducted as part of the development of linagliptin as monotherapy), one Phase 2 study (also part of the monotherapy development program), and 6 Phase 3 studies, 2 of which were long-term extensions (see Table below). At the time of this NDA submission, 10 of these studies have been completed; for the 3 ongoing studies (1218.20, 1218.40, and 1218.52) results of the planned interim analyses are included. Study 1218.57, which was conducted to show bioequivalence between the European (used in Pivotal Phase 3 Study 1218.46) and US Glucophage® reference products, was also conducted as part of the development of the fixed-dose combination for linagliptin and metformin.
Reviewer's Note: The three BE studies conducted for the proposed FDC tablets performed the comparison of TBM formulations to EU sourced metformin. However, during the IND stage discussions, sponsor was advised to compare their FDC to the US source metformin. The sponsor did conduct BE comparison for EU verus US source metformin (Glucophage®). Therefore, for the NDA as filed, this BE study comparing EU versus US Glucophage® also becomes pivotal.

Based on the established pharmacokinetic, safety, and efficacy profiles of metformin and linagliptin, pivotal Study 1218.46 tested the highest (1000 mg bid) and lowest (500 mg bid) doses of metformin hydrochloride alone and with linagliptin 2.5 mg bid with a bracketing approach for the intermediate dose level (850 mg bid metformin hydrochloride alone and in combination with 2.5 mg linagliptin were not tested). The safety and efficacy of the 2.5/850 mg dose of the combination are reliably supported by the data collected in pivotal Study 1218.46 (and its extension, Study 1218.52) with the 2.5/500 mg and 2.5/1000 mg doses and by the data gathered for the 2.5/850 mg dose in supportive Studies 1218.17 and 1218.20.

Study [Reference]	Study Design and Duration	Treatments	N
Phase 1 (Healthy Subjects)			
1218.4 [U06-3414, Module 5.3.1.2]	Randomized, open-label, multiple dose, crossover study	Lina 10 mg qd + Met 850 mg tid	15
1218.47 [U09-2346, Module 5.3.1.2]	Randomized, open-label, single-dose, crossover, relative bioavailability study	Lina 2.5 mg/Met 1000 mg vs Lina 2.5mg+Met 1000 mg	20
1288.1 [U10-2278 , Module 5.3.1.2]	Randomized, open-label, single-dose, cross-over, pivotal bioequivalence study	Lina 2.5 mg/Met 1000 mg Lina 2.5 mg+Met 1000 mg	96
1288.2 [U10-2276, Module 5.3.1.2]	Randomized, open-label, single-dose, cross-over, pivotal bioequivalence study	Lina 2.5 mg/Met 500 mg vs Lina 2.5 mg+Met 500 mg	95
1288.3 [U10-2303, Module 5.3.1.2]	Randomized, open-label, single-dose, cross-over, pivotal bioequivalence study	Lina 2.5 mg/Met 850 mg vs Lina 2.5 mg+Met 850 mg	96
1288.4 [U10-2236, Module 5.3.1.1]	Randomized, open-label, single-dose, cross-over, kinetic food interaction study	Lina 2.5 mg/Met 1000 mg with and without food	32
		Total Subjects in Phase 1	**354**
Phase II			
1218.6 [U08-1056. Module 5.3.5.1]	12-week, randomized, double-blind, placebo-controlled, parallel-group study with metformin as background	Placebo Lina 5 + Met Lina 10 mg + Met Glimepiride + Met	71 66 66 65
Phase III			
1218.17 [U09-2533, Module 5.3.5.1]	24-week, randomized, double-blind, placebo-controlled study with metformin as background	Placebo + Met Lina 5 + Met	177 523
1218.18 [U09-2458. Module 5.3.5.1]	24-week, randomized, double-blind, placebo-controlled, parallel-group, with metformin as background	Placebo + Met + SU Lina 5 mg + Met + SU	263 792
1218.20 [U10-1465, Module 5.3.5.1]	2-year, randomized, double-blind, active-controlled (glimepiride), parallel-group, with metformin as background	Glimepiride + Met Lina 5 mg + Met	781 778
1218.40 [U10-1468, Module 5.3.5.1]	78-week, open-label extension of Studies 1218.17 and 1218.18 with metformin as background	Lina 5 + Met Lina 5 + Met + SU	610 726
1218.46 [U10-2372 , Module 5.3.5.1]	Pivotal, 24-week, randomized, double-blind, placebo-controlled, factorial design, with treatment naïve or washout	Placebo Met 500 mg Met 1000 mg Lina 2.5 mg + Met 500 mg Lina 2.5 mg + Met 1000 mg Lina 5.0 mg Lina 2.5 + met 1000 open-label	72 144 147 143 143 142 66
1218.52 [U10-2442 Module 5.3.5.1]	54-week, randomized, double-blind, active-controlled, extension of Study 1218.46	Met 1000 mg Lina 2.5 mg +Met 500 mg Lina 2.5 mg + Met 1000	170 225 171
		Total that received L+M included in safety analyses (Phases II and III)	**3084***

Lina=linagliptin; met=metformin; SU=sulfonylurea;
Lina+Met designates combination dosing with separate linagliptin and metformin tablets (free combination).
Lina/Met designates a single tablet containing linagliptin and metformin (fixed-dose combination).
* Note: Patients from various treatment arms continued into the extension studies; it is not possible to simply add numbers in the column to derive the total of 3084.

Efficacy Overview:

The primary efficacy analysis results are mentioned in the table below:

Analysis group/ study	Treatment	N	Adjusted mean % difference from baseline to endpoint[a] in HbA_{1c}	Adjusted mean % (SE) difference between L+M and comparator arm[b]	Comparative results and statistic (P; CI[c])
PIVOTAL STUDY					
EFF-1 1218.46	Double-blind		Double-blind	Double-blind	
	L+M 2.5/1000	140	-1.59	-0.51 (0.11)	L+M 2.5/1000 superior to Met 1000; P<0.0001; -0.73, -0.30
	M1000	138	-1.07		
	L+M 2.5/1000	140	-1.59	-1.14 (0.11)	L+M 2.5/1000 superior to L5; P<0.0001; -1.36, -0.92
	L5	135	-0.45		
	L+M 2.5/500	137	-1.22	-0.58 (0.11)	L+M 2.5/500 superior to Met 500; P<0.0001; -0.79, -0.36
	M 500	141	-0.64		
	L+M 2.5/500	137	-1.22	-0.77 (0.11)	L+M 2.5/500 superior to L5; P<0.0001; -0.99, -0.55
	L5	135	-0.45		
EFF-2a 1218.17	L5+Met bgrd	513	-0.49	-0.64 (0.07)	Linagliptin 5 added to Met superior to placebo added to Met; P<0.0001; -0.78, -0.50
	Placebo +Met bgrd	175	+0.15		
EFF-3a 1218.20	L5+Met bgrd	766	-0.38	0.22 (0.04)	Linagliptin 5 added to Met non-inferior at the 0.35% level to glimepiride added to Met; reduction with glimepiride 0.22% greater; P=0.0007; 0.13, 0.31
	Glimepiride +Met bgrd	761	-0.60		

Note: bgrd=background

[a] Endpoint for 1218.46 and 1218.17 was 24 weeks; for 1218.20 it was 52 weeks (interim analysis);

[b] Negative value indicates greater reduction with L+M.

[c] Confidence Interval was 95% for 1218.46 and 1218.17; 97.5% for 1218.20

Note: Results are for the FAS (LOCF) for all 3 studies

Safety Overview:

Among all patients treated with L+M in Phase II and III studies, 2218 (71.9%) experienced one or more AEs, 4 (0.1%) died, 239 (7.7%) had SAEs, and 130 (4.2%) discontinued because of AEs.

Group	Any AE		Death		SAE		Discontinuations for AEs	
	L+M	Comp[a]	L+M	Comp[a]	L+M	Comp[a]	L+M	Comp[a]
All L+M patients[b]								
SAF-1[b]	2218 (71.9)	NA	4 (0.1)	NA	239 (7.7)	NA	130 (4.2)	NA
L+M vs placebo or monotherapies with L or M (24 weeks)								
SAF-2	145 (50.7)[c]	38 (52.8)[d] 78 (54.9)[e] 144 (49.5)[f]	0	0[d] 0[e] 1 (0.3)[f,g]	4 (1.4)[c]	1 (1.4)[d] 3 (2.1)[e] 9 (3.1)[f]	8 (2.8)[c]	5 (6.9)[d] 6 (4.2)[e] 9 (3.1)[f]
SAF-4	283 (54.1)	101 (57.1)	0	0	18 (3.4)	5 (2.8)	9 (1.7)	4 (2.3)
SAF-6	428 (52.9)	245 (52.4)	0	1 (0.2)[g]	22 (2.7)	14 (3.0)	17 (2.1)	13 (2.8)
L+M vs placebo+metformin long-term, double-blind[b]								
SAF-3	86 (60.1)[h] 91 (63.6)[j]	91 (61.9)	0[h] 1 (0.7)[j]	1 (0.7)[g]	3 (2.1)[h] 4 (2.8)[j]	7 (4.8)	6 (4.2)[h] 7 (4.9)[j]	9 (6.1)
L+M vs glimepiride+metformin; or L+M+SU vs placebo+M+SU								
SAF-5[b]	611 (78.5)	662 (84.8)	2 (0.3)	3 (0.4)	93 (12.0)	114 (14.6)	45 (5.8)	77 (9.9)
SAF-7[k]	528 (66.7)	158 (60.1)	0	0	25 (3.2)	11 (4.2)	25 (3.2)	5 (1.9)
Phase I (healthy subjects)								
SAF-8	126 (35.6)	NA	0	NA	0	NA	0	NA

[a] Comparator for SAF-3 was met 1000 monotherapy; for SAF-4, placebo added to met background; for SAF-5, glimepiride added to met background; for SAF-6, met monotherapy; for SAF-7, placebo added to met+SU.

[b] Exposure in SAF-1 and SAF-5 also contribute to assessment of long-term safety

[c] Both doses of L+M combined

[d] Placebo

[e] Linagliptin 5

[f] Metformin (combined doses)

[g] Same death in SAF-2, -3, and -6; patient received metformin 1000 mono in 1218.46

[h] L+M 2.5/500

[j] L+M 2.5/1000

[k] Patients in both arms also received SU as background; treatments were L+M+SU vs placebo+M+SU

Sources: SCS [Module 2.7.4, Tables 2.1.1: 1, 2.2.1: 2, 2.3.1: 1, 2.4.1: 1, 2.5.1: 1, 2.6.1: 1, 2.8.1: 1, 2.9.1: 1]

Bioequivalence Study Results:
1288.1:

Parameter	Test (FDC) N	Reference (individual tablets) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	96	93	106.5	102.8	110.3	14.5
C_{max}	96	93	103.4	100.3	106.7	12.7
Metformin hydrochloride 1000 mg						
$AUC_{0-\infty}$	96	93	103.8	100.2	107.4	14.3
C_{max}	96	93	104.6	100.1	109.2	17.9

Source data: 1288.1 [U10-2278, Module 5.3.1.2, Section 15.5]

1288.2:

Parameter	Test (FDC) N	Reference (individual tablets) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	94	95	99.9	96.6	103.3	13.9
C_{max}	94	95	98.1	94.4	101.9	16.0
Metformin hydrochloride 500 mg						
$AUC_{0-\infty}$	94	95	99.1	96.4	102.0	11.6
C_{max}	94	95	97.9	94.4	101.5	14.9

Source data: 1288.2 [U10-2276, Module 5.3.1.2, Section 15.5]

1288.3:

Parameter	Test (FDC) N	Reference (individual tablets) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	95	94	104.0	100.2	108.0	15.4
C_{max}	95	94	105.9	102.7	109.3	12.9
Metformin hydrochloride 850 mg						
$AUC_{0-\infty}$	95	93	101.2	98.3	104.1	11.8
C_{max}	95	93	99.8	96.2	103.6	15.4

Source data: 1288.3 [U10-2303, Module 5.3.1.2, Section 15.5]

1218.57 (EU vs US Metformin)

Parameter	Test (Merck) N	Reference (BMS) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Metformin 1000 mg						
$AUC_{0-\infty}$	28	28	97.2	91.5	103.3	13.3
C_{max}	28	28	98.4	90.8	106.6	17.7
Metformin 500 mg						
AUC_{0-72}	27	28	102.2	95.7	109.1	14.3
C_{max}	27	28	101.6	91.6	112.8	22.9

Source data: 1218.57 [U09-2155, Module 5.3.1.2, Section 15.5]

Sponsor's Clinical Pharmacology Conclusions:

- PKPD results of 2.5 mg linagliptin BID compare well to 5 mg linagliptin QD and are supportive.
- Dosage adjustments of linagliptin are not recommended on the basis of age, gender, BMI, race, or renal or hepatic impairment.
- No dosage adjustment is recommended based on age, gender, BMI or race for metformin. However, metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced; metformin is contraindicated in patients with renal failure and renal dysfunction (creatinine clearance <60ml/min).
- For the LM combination no dosage adjustment is necessary based on age, gender, BMI/weight or race but due to the metformin component, treatment with the combination should generally be avoided in hepatically impaired patients (hepatic impairment has been associated rarely with lactic acidosis). The LM fixed-dose combination is proposed to be contraindicated in patients with renal impairment (defined as serum creatinine levels of ≥1.5 mg/dL in males and ≥1.4 mg/dL in females, or abnormal creatinine clearance).
- There are no dedicated studies/analyses investigating the effect of a linagliptin/metformin fixed-dose combination tablet on the pharmacokinetics of a third substance or vice versa. Based on the absence of a clinically relevant interaction between linagliptin and metformin and the known data for metformin and linagliptin with regard to drug-drug interactions, sponsor assumed that the same conditions, limitations, and dose adjustments as reported for the single entities will apply to the fixed-dose combination.

Potential Clinical Pharmacology Review Questions:

- What is the nature of dose-response for efficacy and safety with LM and dose it support the proposed dose/dosage regimen?
- Are the to-be-marketed fixed-dose combination formulations of LM bioequivalent to the individual drug products used in pivotal phase 3 trials?
- Is the US approved Glucophage® (metformin HCL) formulation bioequivalent to the European source Glucophage® (metformin HCL) used in pivotal phase 3 trials?
- What is the effect of food on pharmacokinetics of LM?
    - Do the results warrant any dose adjustment?
    - Do the results support sponsor's proposed language?
- What is the nature and extent of interaction, if any, between linagliptin and metformin when co-administered?
    - Does the DDI result warrant for any dose adjustments for LM?
    - Any other additional DDI concern for the FDC besides what is known for the individual drug products?
- Are the bioanalytical methods adequate?
- Are sponsor's assessments for specific populations appropriate and do they adequately support the proposed labeling language for LM?

GRMP Filing Checklist:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 201281 **Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc. **Stamp Date:** 01/19/2011

Drug Name: Linagliptin/Metfomin Fixed-Dose Combination **NDA/BLA Type:** Combination drug product (505(b)(2))

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		To be marketed formulation has not been used in the pivotal clinical trials. Pivotal BE trials compare TBM and Phase 3 individual products.
2	Has the applicant provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X		Sponsor have not submitted electronic raw data files for the BE/BA trials and a request will be communicated in the filing letter
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			**NA**
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		Dose-Response Information is discussed
8	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?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			**NA** Sponsor has requested a waiver from conducting pediatric studies for patients below (b) (4)

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			**NA**
11	Is the appropriate pharmacokinetic information submitted?	**X**		Reports only
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	**X**		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?		**X**	Need to request data
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	**X**		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	**X**		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	**X**		
17	Was the translation from another language important or needed for publication?		**X**	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Manoj Khurana

Reviewing Pharmacologist Date

Sally Choe

Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANOJ KHURANA
10/11/2011

JAYABHARATHI VAIDYANATHAN
10/11/2011

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 201-281 (0000)	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Date:	January 19, 2011, and June 1, 2011		
Division:	DMEP	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Boehringer Ingelheim		
Trade Name:	---	**Date Assigned:**	January 21, 2011, and June 3, 2011
Generic Name:	Linagliptin/Metformin Hydrochloride	**Date of Review:**	September 8, 2011
Indication:	Treatment of patients with type 2 diabetes mellitus	**Type of Submission:** Original NDA and Response to FDA Information Request – CMC Amendment (Sequence 0007)	
Formulation/strengths	Immediate-Release Tablet		
Route of Administration	Oral		
Type of Review	• Dissolution Method and Acceptance Criteria • Manufacturing Site Change		

SUBMISSION:

Boehringer Ingelheim requests the approval of a 505 (b) (2) NDA for linagliptin/metformin hydrochloride fixed dose combination (L/M FDC) tablets for the treatment of type 2 diabetes. Three strengths of the combination product (2.5/500 mg, 2.5/850 mg, and 2.5/1000 mg) have been developed. In all three strengths, the amount of linagliptin is 2.5 mg; the amount of metformin hydrochloride is 500 mg, 850 mg and 1000 mg. Metformin hydrochloride has been approved in the US in dose strengths of 500 mg, 850 mg and 1000 mg for a twice-a-day application. The therapeutic dose of linagliptin as a mono compound is 5 mg once a day. In order to match this regimen, the Applicant split the regimen to two doses of 2.5 mg each. The dosage form is film-coated tablet for oral administration and the dosage regimen is two doses per day.

BIOPHARMACEUTICS:

The focus of the Biopharmaceutics review is to evaluate the information/data supporting the proposed dissolution method, dissolution acceptance criteria, and manufacturing site change and provide a recommendation regarding their acceptability.

Background:

The Applicant performed three bioequivalence studies to compare the TBM Linagliptin/metformin FDC tablets and the individual tablets used in the Phase III pivotal efficacy study. These studies are:

1. **Study 1288.1** was conducted to demonstrate bioequivalence between the highest proposed FDC dose strength (L2.5/M1000) and individual linagliptin tablets (2.5 mg) or EU commercial Glucophage® (metformin) tablets (1000 mg). Test and reference products were analyzed by comparative dissolution testing in three different media (pH 1, 4.5, and 6.8) using the proposed dissolution method for linagliptin / metformin hydrochloride film-coated tablets.

2. **Study 1288.2** was conducted to demonstrate bioequivalence between the lowest proposed FDC dose strength (L2.5/M500) and individual linagliptin tablets (2.5 mg) or EU commercial Glucophage® (metformin) tablets (500 mg). Test and reference products were analyzed by comparative dissolution testing in three different media (pH 1, 4.5, and 6.8) using the proposed dissolution method for linagliptin / metformin hydrochloride film-coated tablets.

3. **Study 1218.57** was conducted to demonstrate bioequivalence between Glucophage from Merck and Glucophage from BMS at the dose strength of 500 mg and 1000 mg. Metformin hydrochloride tablets (Glucophage®) sourced from the US and EU market and tested in the bioequivalence study 1218.57 were also compared by dissolution testing.

In addition, the Applicant performed another bioequivalence study (**Study 1288.3**) to compare the to-be-marketed L/M FDC tablets and the individual tablets at the intermediate dose strength of L2.5/M850 in order to demonstrate bioequivalence between the FDC dose strength (L2.5/M850) and individual linagliptin tablets (2.5 mg) or EU commercial Glucophage® (metformin) tablets (850 mg). Additionally, the Applicant performed dissolution testing using the proposed method to demonstrate comparability between US commercial Glucophage®and EU commercial Glucophage®tablets at dose strength of 850 mg.

Furthermore, the first three production scale batches for each of the dosage strengths (primary stability batches) were compared by *in vitro* dissolution with linagliptin/metformin hydrochloride tablet batches tested in bioequivalence studies 1288.1, 1288.2, and 1288.3.

Formulation:
The composition of the formulation for the proposed drug product is given in Table 1 below.

Table 1: Qualitative and quantitative composition of linagliptin/metformin hydrochloride film-coated tablets

		linagliptin / metformin hydrochloride		
		2.5 mg / 500 mg	**2.5 mg / 850 mg**	**2.5 mg / 1000 mg**
Ingredient	**Function**	**[mg/ tablet]**	**[mg/ tablet]**	**[mg/ tablet]**
Linagliptin	Active ingredient	2.500	2.500	2.500
Metformin hydrochloride	Active ingredient	500.000	850.000	1000.000
Arginine	(b) (4)			
Corn starch				
Copovidone				
Colloidal silicon dioxide				
Magnesium stearate				
(b) (4)				
Titanium dioxide				
Yellow ferric oxide				
Red ferric oxide				
Propylene glycol				
Hypromellose (b) (4)				
Talc				
(b) (4)				
	Total weight (film coated tablet)	**602.0**	**1016.0**	**1198.0**

(b) (4)

Proposed Dissolution Method and Acceptance Criteria

Both linagliptin and metformin hydrochloride (HCl) show high solubility (> 1 mg/ml) in aqueous media over the entire physiological pH range from pH1 to pH 8.0. The Applicant classified linagliptin and metformin hydrochloride as class III compounds providing high solubility and low permeability according to the Biopharmaceutics Classification System (BCS).

The Applicant investigated the conditions to establish the proposed dissolution test method and the associated acceptance criteria [i.e., apparatus, rotation speed, dissolution media, discriminating ability (b) (4) (b) (4) storage conditions), and justification of dissolution acceptance criteria]. APPENDIX 1 (pages 6-41) includes the details for the development and validation of the proposed dissolution test and the setting of the acceptance criteria for both linagliptin and metformin HCl.

Based on the provided information/data the selected dissolution method parameters and dissolution acceptance criteria are as follows:

Apparatus: Paddle (Apparatus 2)
Agitation: 50 rpm
Medium: 900 mL 0.1 M HCl
Temperature: 37°C
Sampling time: 30 minutes
Proposed Acceptance Criteria: "Q = (b) (4) at 30 minutes for linagliptin and metformin HCl"

Reviewer's Note:
The provided data support the proposed dissolution method and acceptance criteria and they are acceptable.

Comparative Dissolution Testing using Metformin Products Sourced in US and EU

The Applicant compared the in-vitro dissolution of metformin hydrochloride (Glucophage®) 500 mg and 1000 mg sourced from the US and EU market using the proposed dissolution method (Paddle, 50 rpm, 900 mL 0.1 M HCl). The Applicant tested these products in the bioequivalence study 1218.57.

The comparative dissolution profiles are shown in the next Figure. Both dosage strengths sourced from the US and EU met the bioequivalence criteria in study 1218.57. The calculated f_2 factor for the 500 mg is < 50 indicating no similarity. However, the calculated f_2 factor for the 1000 mg is ≥ 50 indicating similarity and in accordance with the bioequivalence results of study 1218.57.

Comparison of metformin HCl batches (EU vs. US commercial batches) tested in study 1218.57, 500 mg, pH 1 (Paddle, 50 rpm, 900 mL 0.1 M HCl, n=12)

500 mg **1000 mg**

Reviewer's Note:
It should be noted that the similarity f2 failure for the 500 mg tablet is bio-irrelevant, because it is superseded by the in vivo results from the BE study indicating that products manufactured by drug substance from both sources (US and EU) met the bioequivalence criteria in study 1218.57.

Manufacturing Site Change
The manufacturing process of linagliptin/metformin hydrochloride film-coated tablets was developed initially at Boehringer Ingelheim's site in Biberach, Germany, and then transferred to the intended commercial manufacturing site of Boehringer Ingelheim in Ingelheim, Germany. The production site Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim is the intended commercial manufacturing site.

The Applicant reported that the same composition, design and operating principle of equipment, and the same general manufacturing process have been utilized throughout pharmaceutical development, including manufacture of the clinical trial batches at the Biberach manufacturing site, manufacture of the primary stability batches, and manufacture of clinical trial batches at the production site in Ingelheim. The Applicant stated that only minor process adaptations were made during the transfer from the R&D site Boehringer Ingelheim, Biberach, Germany, to the commercial manufacturing site Boehringer Ingelheim, Ingelheim, Germany. The adaptations performed on equipment size and layout (b) (4) to optimize the commercial manufacturing process.

The Applicant generated comparative dissolution profiles of linagliptin / metformin HCl film-coated tablets manufactured at R&D site Boehringer Ingelheim, Biberach and at manufacturing site Boehringer Ingelheim, Ingelheim. Linagliptin / metformin hydrochloride film-coated tablet batches for clinical trials were manufactured at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, and at Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, which is the proposed commercial site. The dissolution profiles of drug product batches of the dosage strength 2.5/1000 mg manufactured at the different sites are shown in the next Figure.

Dissolution profiles of linagliptin/metformin hydrochloride film-coated tablets 2.5 mg/1000 mg, (Paddle apparatus, 50 rpm, 900 mL, 0.1 M hydrochloric acid, n=12)

Linagliptin	Metformin HCl
(b) (4)	

Reviewer's Note:
The results show that the dissolution profiles are not affected by the transfer to the intended commercial manufacturing site. Therefore, from the Biopharmaceutics perspective the proposed site change is acceptable.

RECOMMENDATION:

ONDQA-Biopharmaceutics has evaluated the provided Biopharmaceutics information/data and has the following recommendations:

1. Dissolution Method and Acceptance Criteria:

The following proposed dissolution method parameters and dissolution criteria for the evaluation of linagliptin and metformin HCl are found acceptable.

Apparatus: Paddle (Apparatus 2)
Agitation: 50 rpm
Medium: 900 mL 0.1 M HCl
Temperature: 37°C
Sampling time: 30 minutes
Acceptance Criteria: Q = (b) (4) at 30 minutes for Linagliptin
Q = (b) (4) at 30 minutes for Metformin HCl

2. Proposed Manufacturing Site Change:

The provided dissolution data support the proposed manufacturing site change. From the Biopharmaceutics view point the Applicant's request for a manufacturing site change is acceptable.

OVERALL ASSESSMENT:

From the Biopharmaceutics perspective NDA 201-281 for Linagliptin/Metformin Hydrochloride tablets is recommended for approval.

Signature
Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc: KSharma, MHai, SMarkofsky, STran

APPENDIX 1

Dissolution Method and Acceptance Criteria

The Applicant investigated the following conditions to establish the proposed dissolution test method and the associated acceptance criteria.

Apparatus and Rotation Speed

The Applicant evaluated formulations using the Paddle apparatus at the rotation speeds of 50 and (b) (4) and the Basket apparatus at 50, (b) (4). The Applicant reported that the Basket apparatus at 50 and (b) (4) exhibit high variances up to 30 minutes whereas the results at (b) (4) are comparable to results measured with the Paddle apparatus at 50 rpm (see Figure 1- Figure 2). Although the results of the Paddle apparatus at 50 show higher variances for early time points compared to a rotation speed of (b) (4) the Applicant selected the Paddle apparatus at 50 rpm to achieve slower dissolution profile and possibly more discriminatory power (see Figure 3- Figure 4).

Figure 1: Influence of rotation speed using the Basket apparatus, linagliptin (900 mL, pH 1, n=6)

Figure 2: Influence of rotation speed using the Basket apparatus, metformin hydrochloride (900 mL, pH 1, n=6)

Figure 3: Influence of rotation speed using the Paddle apparatus, linagliptin (900 mL, pH 1, n=6)

Figure 4: Influence of rotation speed using the Paddle apparatus, metformin hydrochloride (900 mL, pH 1, n=6)

Dissolution Medium

The Applicant generated dissolution profiles of linagliptin/metformin hydrochloride film-coated tablets using the Paddle apparatus with a rotation speed of 50 rpm and a volume of 900 mL of various dissolution media (0.1 M HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8. The amounts dissolved of linagliptin and metformin hydrochloride are comparable in all media tested (see Figure 5 – Figure 6).

Figure 5: Dissolution profile comparison in different media, linagliptin 2.5/1000 mg (Paddle, 50 rpm, 900 mL, n=12)

Figure 6: Dissolution profile comparison in different media, metformin hydrochloride, 2.5/1000 (Paddle, 50 rpm, 900 mL, n=12)

The Applicant stated that Hydrochloric acid (0.1 M) was selected due to its relatively higher discriminatory power as compared to the other two media, and because it is expected that dissolution will occur mostly in stomach.

Discriminatory Power
The following variables were selected to investigate the discriminatory power of the proposed method: quantitative and qualitative composition of tablet formulation, (b) (4) storage conditions. The proposed dissolution method using the Paddle apparatus at 50 rpm and 900 mL 0.1 M HCl was used to evaluate the different variables.

1. Quantitative and qualitative composition of tablet formulations

The different compositions are qualitatively similar except for the colors. The Applicant compared the dissolution profiles of different dosage strengths of linagliptin/metformin hydrochloride film-coated tablets and the results show that the dissolution profiles are almost superimposed (see Figure 7 - Figure 8).

Figure 7: Comparison of different dosage strengths, linagliptin (Paddle, 50 rpm, 900 mL pH 1, n=12)

(b) (4)

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5. Storage conditions

The Applicant evaluated primary stability batches in HDPE bottles with desiccant (60, 180, and 2000 counts) stored for 6 months at 40 °C/75% r h. as well as 12 months (60 and 180 counts) and 9 months (2000 counts) at 25° C/60% r.h. The Applicant reported slight changes in the dissolution profiles in the following tested batches, but a (b) (4) dissolution after 30 minutes was always achieved:
-2.5 mg / 500 mg dosage strength in 2000 counts HDPE bottles with desiccant at 40°C/75 % r h. (see Figure 16 and Figure 17).
- 2.5 mg / 850 mg dosage strength in 2000 counts HDPE bottles with desiccant at 25°C/60 % r.h. and 40°C/75 % r h. (see Figure 18 and Figure 19).
- 2.5 mg / 1000 mg dosage strength in 60 counts HDPE bottles with desiccant at 25°C/60 % r.h. and 40°C/75 % r h. (see Figure 20 and Figure 21) and in 180 and 2000 counts HDPE bottles with desiccant at 40°C/75 % r.h. (see Figure 22 - Figure 25).

Figure 16: Primary stability, HDPE bottle (2000 counts), linagliptin, 2.5 mg/500 mg

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Figure 25: Primary stability, HDPE (2000 counts), metformin hydrochloride, 2.5 mg/1000 mg

Reviewer's Note:

The data obtained examining the influence of the tested variables (quantitative and qualitative composition of tablet formulation, (b) (4), storage conditions) to assess the discriminatory power of the proposed method (Paddle apparatus at 50 rpm and 900 mL 0.1 M HCl) show that the proposed dissolution method is discriminating.

Justification of the Dissolution Acceptance Criteria

Initially, the Applicant proposed a dissolution acceptance criterion of Q= (b) (4) in 30 minutes for each active ingredient. The Applicant stated that the proposed acceptance criteria are based on ICH Q6A for high solubility drug substances throughout the physiological range, and the results obtained of batches used in pivotal clinical studies and primary stability studies.

The analytical procedures used for the dissolution test of linagliptin/metformin hydrochloride film-coated tablets, 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg tablets were validated with respect to specificity, linearity, accuracy, repeatability, intermediate precision, and robustness. The linagliptin samples were analyzed by HPLC-UV (b) (4) and the metformin hydrochloride samples were analyzed by UV-spectrophotometry (b) (4) The analytical procedures are suitable for routine quality control.

The Filing Communication dated March 31, 2011 included an FDA comment which requested the Applicant to change the dissolution acceptance criteria from Q= (b) (4) in 30 minutes to NLT (b) (4) in 20 minutes. In response to FDA comment, the Applicant requested on June 1, 2011, a dissolution acceptance criterion of Q = (b) (4) for both active ingredients at 30 minutes. The Applicant stated that Q= (b) (4) will require not less than (b) (4) dissolved for each individual tablet at (b) (4) dissolution testing. The Applicant stated that they inferred that FDA's comment is about the average percent dissolved at (b) (4) dissolution testing, where Q= (b) (4) requires the average of 12 tablets (b) (4) to be not less than (b) (4) dissolved.

The Applicant provided the following rationale for the requested dissolution acceptance criteria of Q = (b) (4)

dissolved at 30 minutes for linagliptin / metformin hydrochloride film-coated tablets 2.5 mg / 500 mg, 2.5 mg / 850 mg, and 2.5 mg / 1000 mg / tablet:

- High dissolution variability at early time points which could lead to an unwarranted batch rejection
- In vivo bioavailability of both compounds is independent from their dissolution characteristics

In support of the second bullet above, the Applicant stated that they have conducted a relative bioavailability study (study 1288.6) to further investigate the relationship of in vitro dissolution and in vivo bioavailability of linagliptin and metformin hydrochloride. The Applicant submitted a short summary of the study results given in Appendix A. In this study, linagliptin / metformin hydrochloride film-coated tablets 2.5 mg / 1000 mg with different dissolution behavior were tested (see Figure 26-27 and Table 2-5). The test batch is the same batch as used in the pivotal bioequivalence study 1288.1 which exhibits a standard dissolution profile whereas the reference batch exhibits a slower dissolution profile (f_2 value: 34 for both active ingredients). The results of this study show that for linagliptin and metformin hydrochloride the 90 % confidence intervals for both AUC and C_{max} met the bioequivalence acceptance criteria of 80-125 %.

The Applicant stated that the slow releasing batch tested in study 1288.6 shows a mean of (b) (4) dissolved (linagliptin/metformin hydrochloride) at 20 minutes. Individual values are even below (b) (4) dissolved (see Table 3 and 5). Therefore, this reference batch would not comply with a acceptance criterion of Q = (b) (4) at 20 minutes and would be rejected even though this batch met the bioequivalence criteria when compared to the pivotal clinical trial batch.

Hence, the Applicant concluded that the differences in the dissolution profile of both active ingredients up to 30 minutes are therefore not bio-relevant, and a Q-value of (b) (4) at 30 minute dissolution time point is a more suitable acceptance criterion to ensure that bioequivalent batches will be released to the market. The slow releasing batch tested in study 1288.6 shows a mean of (b) (4) dissolved (linagliptin/metformin hydrochloride) at 30 minutes. Single values at 30 minutes for this batch are even close to (b) (4) dissolved (see Table 3 and 5). This bioequivalent batch would comply with (b) (4) dissolution testing, if the specification is set at 30 minutes with Q = (b) (4)

Figure 26: Comparison of a fast and slow releasing batch tested in study 1288.6, linagliptin, 2.5 mg/1000 mg (paddle, 50 rpm, 900 mL pH 1, n=12)

Figure 27: Comparison of a fast and slow releasing batch tested in study 1288.6, metformin hydrochloride, 2.5 mg/1000 mg (paddle, 50 rpm, 900 mL pH 1, n=12)

Table 2: Clinical batch tested in studies 1288.1 and 1288.6, linagliptin/metformin hydrochloride, 2.5mg/1000 mg, linagliptin, pH 1

Test conditions: Paddle 50 rpm, 900 mL 0.1 M HCl						
Batch No.	**Sample No.**	**% Dissolved at time in minutes**				
		10	**15**	**20**	**30**	**45**
B091003929 (903235)	1	(b) (4)				
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	Mean					
	RSD					

Table 3: Clinical batch tested in study 1288.6, linagliptin/metformin hydrochloride, 2.5mg/1000 mg, linagliptin, pH 1

Test conditions: Paddle 50 rpm, 900 mL 0.1 M HCl						
Batch No.	**Sample No.**	**% Dissolved at time in minutes**				
		10	**15**	**20**	**30**	**45**
B101002992	1	(b) (4)				
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	Mean					
	RSD					

Table 4: Clinical batch tested in studies 1288.1 and 1288.6, linagliptin/metformin hydrochloride, 2.5 mg/1000 mg, metformin hydrochloride, pH 1

Test conditions: Paddle 50 rpm, 900 mL 0.1 M HCl						
Batch No.	**Sample No.**	**% Dissolved at time in minutes**				
		10	**15**	**20**	**30**	**45**
B091003929 (903235)	1	(b) (4)				
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	Mean					
	RSD					

Table 5: Clinical batch tested in study 1288.6, linagliptin/metformin hydrochloride, 2.5 mg/1000 mg, metformin hydrochloride, pH 1

Test conditions: Paddle 50 rpm, 900 mL 0.1 M HCl						
Batch No.	**Sample No.**	**% Dissolved at time in minutes**				
		10	**15**	**20**	**30**	**45**
B101002992	1	(b) (4)				
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	Mean					
	RSD					

Based on the above, the dissolution method parameters and dissolution acceptance criteria are as follows:

Apparatus: Paddle (Apparatus 2)
Agitation: 50 rpm
Medium: 900 mL 0.1 M HCl
Temperature: 37°C
Sampling time: 30 minutes
Proposed acceptance criteria: "Q = (b) (4) at 30 minutes for Linagliptin and Metformin HCl"

Comparative Dissolution Testing using Bioequivalence Studies Batches

The Applicant performed comparative dissolution testing in three different media (pH 1, 4.5, and 6.8) and 12 tablets of each batch to compare the FDC product tested in bioequivalence studies 1228.1, 1288.2, and 1288.3 and the respective linagliptin and metformin hydrochloride mono products. The Applicant tested bio-batch Batch B091003907 and B091004011 for the 500 and 850 mg dosage strengths, respectively, and batch B091004015 for the 1000 mg dosage strength. The results are shown in Figure 28- Figure 36 for metformin hydrochloride and in Figure 37- Figure 39 for linagliptin. The f2 values are summarized in Table 6 and Table 7.

Figure 28: Comparison Metformin Hydrochloride, 500 mg, pH 1 (Paddle, 50 rpm, 900 mL, 0.1 M HCl, n=12)

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Figure 39: Comparison Linagliptin, all dosage strengths, pH 6.8 (Paddle, 50 rpm, 900 mL buffer pH 6.8, n=12)

Table 6: f_2 values for linagliptin/metformin hydrochloride film-coated tablets with reference to metformin hydrochloride mono tablets

Test product (Batch No.)	Reference product (Batch No.)	pH (medium)	f2 value
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	metformin hydrochloride 500 mg (B091003907)	1	30
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	metformin hydrochloride 850 mg (B091004011)	1	17
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	metformin hydrochloride 1000 mg (B091004015)	1	19
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	metformin hydrochloride 500 mg (B091003907)	4.5	26
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	metformin hydrochloride 850 mg (B091004011)	4.5	14
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	metformin hydrochloride 1000 mg (B091004015)	4.5	15
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	metformin hydrochloride 500 mg (B091003907)	6.8	74
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	metformin hydrochloride 850 mg (B091004011)	6.8	19
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	metformin hydrochloride 1000 mg (B091004015)	6.8	17

Table 7: f_2 values for linagliptin / metformin hydrochloride film-coated tablets with reference to linagliptin mono tablets

Test product (Batch No.)	Reference product (Batch No.)	pH (medium)	f2 value
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	linagliptin 2.5 mg (B081004241)	1	85
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	linagliptin 2.5 mg (B081004241)	1	89
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	linagliptin 2.5 mg (B081004241)	1	64
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	linagliptin 2.5 mg (B081004241)	4.5	58
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	linagliptin 2.5 mg (B081004241)	4.5	63
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	linagliptin 2.5 mg (B081004241)	4.5	81
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	linagliptin 2.5 mg (B081004241)	6.8	52
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	linagliptin 2.5 mg (B081004241)	6.8	75
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	linagliptin 2.5 mg (B081004241)	6.8	63

Metformin hydrochloride 500 mg dosage strength in pH 6.8 met the criteria of $f_2 \geq 50$ indicating the dissolution profiles of reference and test product are similar. However, the f_2 factor is less than 50 for the other two strengths (850 mg and 1000 mg) indicating the dissolution profiles of reference and test product are dissimilar.

Linagliptin in all three tested media met the f_2 factor (≥ 50) indicating similar dissolution profiles of reference and test products.

Reviewer's Note: Overall, the above dissolution results comparing the reference and test products are no relevant, as for NDAs the dissolution profile comparisons between the reference and test products are not needed. Also for metformin HCl, the results clearly show that the dissolution method is product specific and therefore, a different dissolution method is needed for the reference product.

It is noted that the Applicant did not follow the criteria for calculating the f2 factor such as in some cases more than one timepoint (b) (4) dissolved was used, and in some cases the RSD values exceeds the recommended values at the respective sampling time points. This deviation for calculating the f2 factor is not relevant as the dissolution method is not bio-relevant and the similarity of the profile is not critical because the Applicant performed in vivo study, and the reference and test batches met the bioequivalence criteria.

Comparative Dissolution Testing using Production Scale Batches

The Applicant also compared the in-vitro dissolution of the first three production scale batches of each dosage strength (primary stability batches) to linagliptin/metformin hydrochloride tablet batches tested in bioequivalence studies 1288.1, 1288.2, and 1288.3. One production scale batch for each dosage strength was used as bio-batch as

well as primary stability batch. The comparative dissolution testing used the proposed dissolution method (paddle, 50 rpm, 900 mL 0.1 M HCl) using 12 tablets. The batches used are summarized in Table 8.

Table 8: Production scale batches used for comparative dissolution testing

Batch No. (clinical batch No.)	Comments	Dosage strength [mg]
902832 (B091003928)	Primary stability batch/clinical batch 1288.2	2.5 / 500
902833	Primary stability batch	2.5 / 500
902834	Primary stability batch	2.5 / 500
902829	Primary stability batch	2.5 / 850
902831 (B091004101)	Primary stability batch/clinical batch 1288.3	2.5 / 850
903479	Primary stability batch	2.5 / 850
902825	Primary stability batch	2.5 / 1000
903235 (B091003929)	Primary stability batch/clinical batch 1288.1	2.5 / 1000
903236	Primary stability batch	2.5 / 1000

Figure 40- Figure 45 show the comparative dissolution profiles for linagliptin and metformin hydrochloride. Table 9 lists the f_2 factor of each production scale batch with reference to the batches used in bioequivalence studies.

Figure 40: Comparison production scale batches, metformin hydrochloride, 2.5/500 mg, pH 1 (Paddle, 50 rpm, 900 mL 0.1 M HCl, n=12)

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Figure 45: Comparison production scale batches, linagliptin, 2.5/1000 mg, pH 1 (Paddle, 50 rpm, 900 mL 0.1 M HCl, n=12)

Table 9: f2 factor for production scale batches of linagliptin/metformin hydrochloride film-coated tablets

Test product (Batch No.)	Reference product (Batch No.)	f2 value linagliptin	f2 value metformin hydrochloride
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (902833)	linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	60	67
linagliptin / metformin hydrochloride 2.5 mg / 500 mg (902834)	linagliptin / metformin hydrochloride 2.5 mg / 500 mg (B091003928)	65	67
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (902829)	linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	67	54
linagliptin / metformin hydrochloride 2.5 mg / 850 mg (903479)	linagliptin / metformin hydrochloride 2.5 mg / 850 mg (B091004101)	84	60
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (902825)	linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	58	53
linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (903236)	linagliptin / metformin hydrochloride 2.5 mg / 1000 mg (B091003929)	68	60

Metformin hydrochloride and linagliptin results show that each production scale batch compared to reference batches used in the bioequivalence studies met the criteria of f2 ≥ 50 indicating that all batches exhibit similar dissolution profiles.

Comparative Dissolution Testing using Metformin Products Sourced in US and EU

Furthermore, the Applicant compared the in-vitro dissolution of metformin hydrochloride (Glucophage®) 500 mg and 1000 mg sourced from the US and EU market using the proposed dissolution method (Paddle, 50 rpm, 900 mL 0.1 M HCl). The Applicant tested these products in the bioequivalence study 1218.57.

Batch information of Glucophage® film-coated tablets used in the bioequivalence study 1218.57 is provided in Table 10 and Table 11.

Table 10: Glucophage® film-coated tablets 500 mg

Dosage strength	500 mg	500 mg
Clinical batch number	B081002937	B081004715
Supplier batch number	250086	7K28757A
Use of batch	BE study 1218.57	BE study 1218.57
Drug product manufacturer	Merck Santé s.a.s, Lyon, France	Bristol-Myers Squibb Company, Princeton, USA
Active ingredient	**Metformin Hydrochloride**	
Assay	(b) (4)	

Table 11: Glucophage® film-coated tablets 1000 mg

Dosage strength	1000 mg	1000 mg
Clinical batch number	B081002938	B081004714
Supplier batch number	200846	8D2508A
Use of batch	BE study 1218.57	BE study 1218.57
Drug product manufacturer	Merck Santé s.a.s, Lyon, France	Bristol-Myers Squibb Company, Princeton, USA
Active ingredient	**Metformin Hydrochloride**	
Assay	(b) (4)	

The comparative dissolution profiles are shown in Figure 46 and Figure 47. Both dosage strengths sourced from the US and EU met the bioequivalence criteria in study 1218.57. The calculated f_2 factor for the 500 mg is < 50 indicating no similarity. However, the calculated f_2 factor for the 1000 mg is ≥ 50 indicating similarity and in accordance with the bioequivalence results of study 1218.57.

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Reviewer's Note:
The dissolution results are not biorelevant as both sources from the US and EU met the bioequivalence criteria in study 1218.57.

Site Change

The manufacturing process of linagliptin / metformin hydrochloride film-coated tablets was developed initially at Boehringer Ingelheim's site in Biberach, Germany, and then transferred to the intended commercial manufacturing site of Boehringer Ingelheim in Ingelheim, Germany.

The Applicant reported that the same composition, design and operating principle of equipment, and the same general manufacturing process have been utilized throughout pharmaceutical development, including manufacture of the clinical trial batches at the Biberach manufacturing site, manufacture of the primary stability batches, and manufacture of clinical trial batches at the production site in Ingelheim. The production site Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim is the intended commercial manufacturing site.

The Applicant stated that only minor process adaptations were made during the transfer from the R&D site Boehringer
Ingelheim, Biberach, Germany, to the commercial manufacturing site Boehringer Ingelheim, Ingelheim, Germany. The adaptations performed on equipment size and layout (b) (4) to optimize the commercial manufacturing process.

The Applicant generated comparative dissolution profiles of linagliptin / metformin hydrochloride film-coated tablets manufactured at R&D site Boehringer Ingelheim, Biberach and at manufacturing site Boehringer Ingelheim, Ingelheim. Linagliptin / metformin hydrochloride film-coated tablet batches for clinical trials were manufactured at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, and at Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, which is the proposed commercial site. The dissolution profiles of drug product batches of the dosage strength 2.5/1000 mg manufactured at the different sites are shown in Figure 48 and Figure 49.

Figure 48: Dissolution profiles of linagliptin/metformin hydrochloride film-coated tablets 2.5 mg/1000 mg, linagliptin (Paddle apparatus, 50 rpm, 900 mL, 0.1 M hydrochloric acid, n=12)

(b) (4)

Figure 49: Dissolution profiles of linagliptin/metformin hydrochloride film-coated tablets 2.5 mg/1000 mg, metformin hydrochloride (Paddle apparatus, 50 rpm, 900 mL, 0.1 M hydrochloric acid, n=12)

(b) (4)

Reviewer's Note:
The results show that the dissolution profiles are not affected by the transfer to the intended commercial manufacturing site.

APPENDIX 2

Narrative of study 1288.6

Title : Relative bioavailability of two different batches of a 2.5 mg linagliptin / 1000 mg metformin fixed dose combination tablet (FDC) in healthy male and female volunteers (an open-label, randomized, single dose, two-way crossover, Phase I trial).

Objective: To investigate the relative bioavailability of two different batches of a 2.5 mg linagliptin/1000 mg metformin fixed dose combination tablet (FDC) displaying different *in vitro* dissolution characteristics.

Methods: The study was conducted in 40 healthy male and female volunteers according to an open-label, randomized, two-sequence, two-period crossover design. In each of the 2 periods, that were separated by a wash-out period of at least 35 days, the subjects received a single dose of the fixed combination (FDC) of linagliptin and metformin 2.5/1000 mg after a 10 hour overnight fast. The FDC standard batch with standard dissolution characteristics was considered TEST treatment, while the FDC side batch with slower dissolution characteristics was considered REFERENCE treatment. Serial plasma samples for the analysis of linagliptin and metformin were taken over a time period of 72 hours post dose. Pharmacokinetic parameters of linagliptin and metformin were evaluated separately. Two-sided 90% CIs for the intra-subject ratio (as estimated by the geometric mean of the ratio) of each of AUC0-∞ (metformin), AUC0-72 (linagliptin) and Cmax (both analytes) were calculated to determine whether the CIs were contained in the acceptance range of 80-125% for bioequivalence. Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios were calculated. The statistical model was ANOVA on log-transformed parameters including effects for sequence, subjects nested within sequences, period and treatment. CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated.

Results: 40 data sets (20 male, 20 female) were available for non-compartmental analysis for both investigational batches of the fixed dose combination. For both analytes, linagliptin and metformin, geometric mean plasma concentration-time profiles were closely similar between the TEST (standard batch) and REFERENCE (side batch) FDC batches. Geometric mean linagliptin AUC0-72 (inter-subject gCV%) was 179 nM · h (21.6%) for the FDC TEST product
(standard batch) and also 179 nM · h (20.5%) for the FDC REFERENCE product (side batch). Geometric mean linagliptin Cmax values were 5.36 nM (gCV 20.3%) and 5.39 nM (gCV 20.3%) for the FDC TEST (standard batch) and REFERENCE product (side batch), respectively. Median tmax was 3 h, for both products. Geometric mean metformin AUC0-∞ (inter-subject gCV%) was 12400 ng·h/mL (21.2%) for the FDC TEST product (standard batch) and 12300 ng·h/mL (19.9%) for the for the FDC REFERENCE product (side batch). Geometric mean metformin Cmax values were 1790 ng/mL (gCV 23.0%) and 1820 ng/mL (gCV 25.5%) for the FDC TEST (standard batch) and 4.02 h) and 2.00 (0.65 – 4.02 h) for the FDC TEST (standard batch) and REFERENCE product (side batch), respectively. The geometric mean ratios (FDC to individual tablets), 90% confidence intervals and intra-subject CVs of AUC0-72, AUC0-∞ and Cmax were:

Table A: 1 Point estimates and 90% confidence intervals of AUC0-oo (metformin), AUC_{0-72} (linagliptin) and C_{max} (both analytes)

Parameter	Test FDC (standard batch) N	Reference FDC (side batch) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	40	40	100.07	96.07	104.25	10.9
C_{max}	40	40	99.44	94.17	105.00	14.5
Metformin hydrochloride 1000 mg						
$AUC_{0-\infty}$	40	40	100.32	95.66	105.22	12.7
C_{max}	40	40	97.92	92.47	103.70	15.3

Source data: 1288.6

For both linagliptin and metformin, the 90% CIs for both AUC and Cmax were entirely contained in the standard bioequivalence acceptance range of 80-125%. Therefore *in vivo* bioequivalence of the standard and side batches of the FDC product can be concluded, despite of their different *in vitro* dissolution profiles. The outcome of the study is consistent with the BCS Class III categorization of both active components, rendering the in vivo bioavailability of both linagliptin and metformin independent from their dissolution characteristics (i.e. bioavailability is exclusively governed by permeability characteristics) The intra-individual variability observed for both analytes in this trial was overall low and consistent with previous BA/BE trial results.

Conclusion: It is concluded that L/M FDC batches (2.5/1000 mg) display similar *in vivo* performance characteristics and hence, were demonstrated being bioequivalent despite of their different *in vitro* dissolution characteristics.

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/s/

HOUDA MAHAYNI
09/19/2011

ANGELICA DORANTES
09/19/2011

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	201281	Brand Name	Linagliptin/Metformin FDC
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Linagliptin, Metformin hydrochloride
Medical Division	DMEP	Drug Class	Anti-diabetic (Type 2 Diabetes)
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	Indicated for the treatment of Type 2 Diabetes Mellitus.
		Dosage Form	Film-coated Tablets 2.5 mg Linagliptin(L) / 500 mg Metformin (M), 2.5 mg L / 850 mg M, and 2.5 mg L / 1000 mg M film-coated, IR, (b) (4) tablets
OCP Team Leader	Sally Choe, Ph.D.	Dosing Regimen	One tablet twice daily
Date of Submission	January 19, 2011	Route of Administration	Oral
Estimated Due Date of OCP Review	September 7, 2011	Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
PDUFA Due Date	November 19, 2011	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X			
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	1		**1218.4**
In-vivo effects of primary drug:	**X**			**1218.4**
In-vitro:	**X**	1		**A244/08LU**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	2		**1288.45, 1218.47**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	4		**1288.1, 1288.2, 1288.3, 1288.57**
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	1		**1288.4**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**9**		

Filability		
	"X" if yes	**Comments**
Is Application filable?	**X**	**Comments to the Sponsor:** Please provide raw concentration and PK/PD parameter data (preferably as SAS transport files) for all BE studies (1288.1, 1288.2, 1288.3, 1288.4, and 1218.57) and the PKPD study (1218.45). • The concentration data-set(s) should at least have the following columns: ID, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence. • The PK/PD parameter data set(s) should at minimum have the following columns: ID, Trial Number, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence.
Submission in Brief: See the details below.	**Reviewer's Comments to project manager:** **1. Please send a consult to DSI for inspection of the pivotal BE studies:** **1288.1:** • **Clinical Site and PI:** o **Principal Investigator: Dr Mario Iovino, Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre/Dept. of Clinical Research, Birkendorfer Strasse 65, Biberach, Germany** **1218.57:** • **Clinical Site and PI:** o **Principal Investigator: Dr Mario Iovino, Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre/Dept. of Clinical Research, Birkendorfer Strasse 65, Biberach, Germany** **Bioanalytical Sites for both studies:** (b) (4) **2. From clinical pharmacology we have information requests for the sponsor to be sent in Day-74 letter as highlighted above.**	

#Studies submitted with Analysis Data sets

Submission in Brief:

Sponsor, Boehringer Ingelheim Pharmaceuticals, Inc. has submitted a new drug application for Linagliptin /Metformin hydrochloride (hereafter LM) film-coated fixed-dose combination (FDC) tablets for the treatment of type 2 diabetes mellitus. The proposed indication for LM is "*an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with linagliptin+metformin is appropriate*". The active pharmaceutical ingredients in LM drug product are linagliptin, a dipeptidyl peptidase (DPP4) inhibitor, and metformin HCL, a widely prescribed oral antidiabetic.

LM will be available as three dosage strength immediate-release tablets:

- 2.5 mg Linagliptin / 500 mg Metformin HCL,

- 2.5 mg Linagliptin / 850 mg Metformin HCL, and
- 2.5 mg Linagliptin / 1000 mg Metformin HCL.

The proposed recommended daily dose of LM is one tablet taken twice daily.

Pharmacokinetics, safety, and efficacy profiles of linagliptin monotherapy have been evaluated in the studies reported in NDA 201280, currently under review by the agency. The clinical development program for linagliptin+metformin FDC consists of 13 clinical studies: six Phase I studies (one of these, 1218.4, was conducted as part of the development of linagliptin as monotherapy), one Phase 2 study (also part of the monotherapy development program), and 6 Phase 3 studies, 2 of which were long-term extensions (see Table below). At the time of this NDA submission, 10 of these studies have been completed; for the 3 ongoing studies (1218.20, 1218.40, and 1218.52) results of the planned interim analyses are included. Study 1218.57, which was conducted to show bioequivalence between the European (used in Pivotal Phase 3 Study 1218.46) and US Glucophage® reference products, was also conducted as part of the development of the fixed-dose combination for linagliptin and metformin.
Reviewer's Note: The three BE studies conducted for the proposed FDC tablets performed the comparison of TBM formulations to EU sourced metformin. However, during the IND stage discussions, sponsor was advised to compare their FDC to the US source metformin. The sponsor did conduct BE comparison for EU verus US source metformin (Glucophage®). Therefore, for the NDA as filed, this BE study comparing EU versus US Glucophage® also becomes pivotal.

Based on the established pharmacokinetic, safety, and efficacy profiles of metformin and linagliptin, pivotal Study 1218.46 tested the highest (1000 mg bid) and lowest (500 mg bid) doses of metformin hydrochloride alone and with linagliptin 2.5 mg bid with a bracketing approach for the intermediate dose level (850 mg bid metformin hydrochloride alone and in combination with 2.5 mg linagliptin were not tested). The safety and efficacy of the 2.5/850 mg dose of the combination are reliably supported by the data collected in pivotal Study 1218.46 (and its extension, Study 1218.52) with the 2.5/500 mg and 2.5/1000 mg doses and by the data gathered for the 2.5/850 mg dose in supportive Studies 1218.17 and 1218.20.

Study [Reference]	Study Design and Duration	Treatments	N
Phase 1 (Healthy Subjects)			
1218.4 [U06-3414, Module 5.3.1.2]	Randomized, open-label, multiple dose, crossover study	Lina 10 mg qd + Met 850 mg tid	15
1218.47 [U09-2346, Module 5.3.1.2]	Randomized, open-label, single-dose, crossover, relative bioavailability study	Lina 2.5 mg/Met 1000 mg vs Lina 2.5mg+Met 1000 mg	20
1288.1 [U10-2278 , Module 5.3.1.2]	Randomized, open-label, single-dose, cross-over, pivotal bioequivalence study	Lina 2.5 mg/Met 1000 mg Lina 2.5 mg+Met 1000 mg	96
1288.2 [U10-2276, Module 5.3.1.2]	Randomized, open-label, single-dose, cross-over, pivotal bioequivalence study	Lina 2.5 mg/Met 500 mg vs Lina 2.5 mg+Met 500 mg	95
1288.3 [U10-2303, Module 5.3.1.2]	Randomized, open-label, single-dose, cross-over, pivotal bioequivalence study	Lina 2.5 mg/Met 850 mg vs Lina 2.5 mg+Met 850 mg	96
1288.4 [U10-2236, Module 5.3.1.1]	Randomized, open-label, single-dose, cross-over, kinetic food interaction study	Lina 2.5 mg/Met 1000 mg with and without food	32
		Total Subjects in Phase 1	**354**
Phase II			
1218.6 [U08-1056. Module 5.3.5.1]	12-week, randomized, double-blind, placebo-controlled, parallel-group study with metformin as background	Placebo Lina 5 + Met Lina 10 mg + Met Glimepiride + Met	71 66 66 65
Phase III			
1218.17 [U09-2533, Module 5.3.5.1]	24-week, randomized, double-blind, placebo-controlled study with metformin as background	Placebo + Met Lina 5 + Met	177 523
1218.18 [U09-2458. Module 5.3.5.1]	24-week, randomized, double-blind, placebo-controlled, parallel-group, with metformin as background	Placebo + Met + SU Lina 5 mg + Met + SU	263 792
1218.20 [U10-1465, Module 5.3.5.1]	2-year, randomized, double-blind, active-controlled (glimepiride), parallel-group, with metformin as background	Glimepiride + Met Lina 5 mg + Met	781 778
1218.40 [U10-1468, Module 5.3.5.1]	78-week, open-label extension of Studies 1218.17 and 1218.18 with metformin as background	Lina 5 + Met Lina 5 + Met + SU	610 726
1218.46 [U10-2372 , Module 5.3.5.1]	Pivotal, 24-week, randomized, double-blind, placebo-controlled, factorial design, with treatment naïve or washout	Placebo Met 500 mg Met 1000 mg Lina 2.5 mg + Met 500 mg Lina 2.5 mg + Met 1000 mg Lina 5.0 mg Lina 2.5 + met 1000 open-label	72 144 147 143 143 142 66
1218.52 [U10-2442 Module 5.3.5.1]	54-week, randomized, double-blind, active-controlled, extension of Study 1218.46	Met 1000 mg Lina 2.5 mg +Met 500 mg Lina 2.5 mg + Met 1000	170 225 171
		Total that received L+M included in safety analyses (Phases II and III)	**3084***

Lina=linagliptin; met=metformin; SU=sulfonylurea;
Lina+Met designates combination dosing with separate linagliptin and metformin tablets (free combination).
Lina/Met designates a single tablet containing linagliptin and metformin (fixed-dose combination).
* Note: Patients from various treatment arms continued into the extension studies; it is not possible to simply add numbers in the column to derive the total of 3084.

Efficacy Overview:

The primary efficacy analysis results are mentioned in the table below:

Analysis group/ study	Treatment	N	Adjusted mean % difference from baseline to endpoint[a] in HbA_{1c}	Adjusted mean % (SE) difference between L+M and comparator arm[b]	Comparative results and statistic (P; CI[c])
PIVOTAL STUDY					
EFF-1 1218.46	Double-blind		Double-blind	Double-blind	
	L+M 2.5/1000	140	-1.59	-0.51 (0.11)	L+M 2.5/1000 superior to Met 1000; P<0.0001; -0.73, -0.30
	M1000	138	-1.07		
	L+M 2.5/1000	140	-1.59	-1.14 (0.11)	L+M 2.5/1000 superior to L5; P<0.0001; -1.36, -0.92
	L5	135	-0.45		
	L+M 2.5/500	137	-1.22	-0.58 (0.11)	L+M 2.5/500 superior to Met 500; P<0.0001; -0.79, -0.36
	M 500	141	-0.64		
	L+M 2.5/500	137	-1.22	-0.77 (0.11)	L+M 2.5/500 superior to L5; P<0.0001; -0.99, -0.55
	L5	135	-0.45		
EFF-2a 1218.17	L5+Met bgrd	513	-0.49	-0.64 (0.07)	Linagliptin 5 added to Met superior to placebo added to Met; P<0.0001; -0.78, -0.50
	Placebo +Met bgrd	175	+0.15		
EFF-3a 1218.20	L5+Met bgrd	766	-0.38	0.22 (0.04)	Linagliptin 5 added to Met non-inferior at the 0.35% level to glimepiride added to Met; reduction with glimepiride 0.22% greater; P=0.0007; 0.13, 0.31
	Glimepiride +Met bgrd	761	-0.60		

Note: bgrd=background

[a] Endpoint for 1218.46 and 1218.17 was 24 weeks; for 1218.20 it was 52 weeks (interim analysis);

[b] Negative value indicates greater reduction with L+M.

[c] Confidence Interval was 95% for 1218.46 and 1218.17; 97.5% for 1218.20

Note: Results are for the FAS (LOCF) for all 3 studies

Safety Overview:

Among all patients treated with L+M in Phase II and III studies, 2218 (71.9%) experienced one or more AEs, 4 (0.1%) died, 239 (7.7%) had SAEs, and 130 (4.2%) discontinued because of AEs.

Group	Any AE		Death		SAE		Discontinuations for AEs	
	L+M	Comp[a]	L+M	Comp[a]	L+M	Comp[a]	L+M	Comp[a]
All L+M patients[b]								
SAF-1[b]	2218 (71.9)	NA	4 (0.1)	NA	239 (7.7)	NA	130 (4.2)	NA
L+M vs placebo or monotherapies with L or M (24 weeks)								
SAF-2	145 (50.7)[c]	38 (52.8)[d] 78 (54.9)[e] 144 (49.5)[f]	0	0[d] 0[e] 1 (0.3)[f,g]	4 (1.4)[c]	1 (1.4)[d] 3 (2.1)[e] 9 (3.1)[f]	8 (2.8)[c]	5 (6.9)[d] 6 (4.2)[e] 9 (3.1)[f]
SAF-4	283 (54.1)	101 (57.1)	0	0	18 (3.4)	5 (2.8)	9 (1.7)	4 (2.3)
SAF-6	428 (52.9)	245 (52.4)	0	1 (0.2)[g]	22 (2.7)	14 (3.0)	17 (2.1)	13 (2.8)
L+M vs placebo+metformin long-term, double-blind[b]								
SAF-3	86 (60.1)[h] 91 (63.6)[j]	91 (61.9)	0[h] 1 (0.7)[j]	1 (0.7)[g]	3 (2.1)[h] 4 (2.8)[j]	7 (4.8)	6 (4.2)[h] 7 (4.9)[j]	9 (6.1)
L+M vs glimepiride+metformin; or L+M+SU vs placebo+M+SU								
SAF-5[b]	611 (78.5)	662 (84.8)	2 (0.3)	3 (0.4)	93 (12.0)	114 (14.6)	45 (5.8)	77 (9.9)
SAF-7[k]	528 (66.7)	158 (60.1)	0	0	25 (3.2)	11 (4.2)	25 (3.2)	5 (1.9)
Phase I (healthy subjects)								
SAF-8	126 (35.6)	NA	0	NA	0	NA	0	NA

[a] Comparator for SAF-3 was met 1000 monotherapy; for SAF-4, placebo added to met background; for SAF-5, glimepiride added to met background; for SAF-6, met monotherapy; for SAF-7, placebo added to met+SU.

[b] Exposure in SAF-1 and SAF-5 also contribute to assessment of long-term safety

[c] Both doses of L+M combined

[d] Placebo

[e] Linagliptin 5

[f] Metformin (combined doses)

[g] Same death in SAF-2, -3, and -6; patient received metformin 1000 mono in 1218.46

[h] L+M 2.5/500

[j] L+M 2.5/1000

[k] Patients in both arms also received SU as background; treatments were L+M+SU vs placebo+M+SU

Sources: SCS [Module 2.7.4, Tables 2.1.1: 1, 2.2.1: 2, 2.3.1: 1, 2.4.1: 1, 2.5.1: 1, 2.6.1: 1, 2.8.1: 1, 2.9.1: 1]

Bioequivalence Study Results:
1288.1:

Parameter	Test (FDC) N	Reference (individual tablets) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	96	93	106.5	102.8	110.3	14.5
C_{max}	96	93	103.4	100.3	106.7	12.7
Metformin hydrochloride 1000 mg						
$AUC_{0-\infty}$	96	93	103.8	100.2	107.4	14.3
C_{max}	96	93	104.6	100.1	109.2	17.9

Source data: 1288.1 [U10-2278, Module 5.3.1.2, Section 15.5]

1288.2:

Parameter	Test (FDC) N	Reference (individual tablets) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	94	95	99.9	96.6	103.3	13.9
C_{max}	94	95	98.1	94.4	101.9	16.0
Metformin hydrochloride 500 mg						
$AUC_{0-\infty}$	94	95	99.1	96.4	102.0	11.6
C_{max}	94	95	97.9	94.4	101.5	14.9

Source data: 1288.2 [U10-2276, Module 5.3.1.2, Section 15.5]

1288.3:

Parameter	Test (FDC) N	Reference (individual tablets) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	95	94	104.0	100.2	108.0	15.4
C_{max}	95	94	105.9	102.7	109.3	12.9
Metformin hydrochloride 850 mg						
$AUC_{0-\infty}$	95	93	101.2	98.3	104.1	11.8
C_{max}	95	93	99.8	96.2	103.6	15.4

Source data: 1288.3 [U10-2303, Module 5.3.1.2, Section 15.5]

1218.57 (EU vs US Metformin)

Parameter	Test (Merck) N	Reference (BMS) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Metformin 1000 mg						
$AUC_{0-\infty}$	28	28	97.2	91.5	103.3	13.3
C_{max}	28	28	98.4	90.8	106.6	17.7
Metformin 500 mg						
AUC_{0-72}	27	28	102.2	95.7	109.1	14.3
C_{max}	27	28	101.6	91.6	112.8	22.9

Source data: 1218.57 [U09-2155, Module 5.3.1.2, Section 15.5]

Sponsor's Clinical Pharmacology Conclusions:

- PKPD results of 2.5 mg linagliptin BID compare well to 5 mg linagliptin QD and are supportive.
- Dosage adjustments of linagliptin are not recommended on the basis of age, gender, BMI, race, or renal or hepatic impairment.
- No dosage adjustment is recommended based on age, gender, BMI or race for metformin. However, metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced; metformin is contraindicated in patients with renal failure and renal dysfunction (creatinine clearance <60ml/min).
- For the LM combination no dosage adjustment is necessary based on age, gender, BMI/weight or race but due to the metformin component, treatment with the combination should generally be avoided in hepatically impaired patients (hepatic impairment has been associated rarely with lactic acidosis). The LM fixed-dose combination is proposed to be contraindicated in patients with renal impairment (defined as serum creatinine levels of ≥1.5 mg/dL in males and ≥1.4 mg/dL in females, or abnormal creatinine clearance).
- There are no dedicated studies/analyses investigating the effect of a linagliptin/metformin fixed-dose combination tablet on the pharmacokinetics of a third substance or vice versa. Based on the absence of a clinically relevant interaction between linagliptin and metformin and the known data for metformin and linagliptin with regard to drug-drug interactions, sponsor assumed that the same conditions, limitations, and dose adjustments as reported for the single entities will apply to the fixed-dose combination.

Potential Clinical Pharmacology Review Questions:

- What is the nature of dose-response for efficacy and safety with LM and dose it support the proposed dose/dosage regimen?
- Are the to-be-marketed fixed-dose combination formulations of LM bioequivalent to the individual drug products used in pivotal phase 3 trials?
- Is the US approved Glucophage® (metformin HCL) formulation bioequivalent to the European source Glucophage® (metformin HCL) used in pivotal phase 3 trials?
- What is the effect of food on pharmacokinetics of LM?
    - Do the results warrant any dose adjustment?
    - Do the results support sponsor's proposed language?
- What is the nature and extent of interaction, if any, between linagliptin and metformin when co-administered?
    - Does the DDI result warrant for any dose adjustments for LM?
    - Any other additional DDI concern for the FDC besides what is known for the individual drug products?
- Are the bioanalytical methods adequate?
- Are sponsor's assessments for specific populations appropriate and do they adequately support the proposed labeling language for LM?

GRMP Filing Checklist:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 201281 **Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc. **Stamp Date:** 01/19/2011

Drug Name: Linagliptin/Metfomin Fixed-Dose Combination **NDA/BLA Type:** Combination drug product (505(b)(2))

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		To be marketed formulation has not been used in the pivotal clinical trials. Pivotal BE trials compare TBM and Phase 3 individual products.
2	Has the applicant provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X		Sponsor have not submitted electronic raw data files for the BE/BA trials and a request will be communicated in the filing letter
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		Dose-Response Information is discussed
8	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?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA Sponsor has requested a waiver from conducting pediatric studies for patients below (b) (4)

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			NA
11	Is the appropriate pharmacokinetic information submitted?	X		Reports only
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?		X	Need to request data
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Manoj Khurana

Reviewing Pharmacologist — Date

Sally Choe

Team Leader/Supervisor — Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

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/s/

MANOJ KHURANA
05/02/2011

SALLY Y CHOE
05/03/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-281 (0000)	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DMEP		
Sponsor:	Boehringer Ingelheim	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Linagliptin/Metformin Hydrochloride Tablets	**Date Assigned:**	January 21, 2011
Indication:	Treatment of patients with type 2 diabetes mellitus	**Date of Review:**	February 28, 2011
Formulation	Immediate-Release Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
January 19, 2011	January 19, 2011	January 21, 2011	November 19, 2011
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications---**FILING REVIEW**		

REVIEW SUMMARY:

This submission is a 505 (b) (2) NDA for linagliptin/metformin hydrochloride fixed dose combination (L/M FDC) tablets for the treatment of patients with type 2 diabetes mellitus. The proposed doses of linagliptin and metformin hydrochloride are 2.5/500 mg, 2.5/850 mg, and 2.5/1000 mg. The dosage form is film-coated tablet for oral administration and the dosage regimen is two doses per day.

The composition of the drug product is given in the following Table 1:

Table 1: Qualitative and quantitative composition of linagliptin/metformin hydrochloride film-coated tablets

		linagliptin / metformin hydrochloride		
		2.5 mg / 500 mg	2.5 mg / 850 mg	2.5 mg / 1000 mg
Ingredient	**Function**	**[mg/ tablet]**	**[mg/ tablet]**	**[mg/ tablet]**
Linagliptin	Active ingredient	2.500	2.500	2.500
Metformin hydrochloride	Active ingredient	500.000	850.000	1000.000
Arginine	(b) (4)			
Corn starch				
Copovidone				
Colloidal silicon dioxide				
Magnesium stearate				
(b) (4)				
Titanium dioxide				
Yellow ferric oxide				
Red ferric oxide				
Propylene glycol				
Hypromellose (b) (4)				
Talc				
(b) (4)				
	Total weight (film coated tablet)	**602.0**	**1016.0**	**1198.0**

(b) (4)

FDA is currently in the process of reviewing the NDA for linagliptin (Ondero®) 5 mg tablets.

Both linagliptin and metformin hydrochloride drug substances show high solubility in aqueous media from pH 1 to pH 8.0. The sponsor classified both linagliptin and metformin hydrochloride as BCS Class III compounds. Various conditions were investigated to establish an appropriate dissolution test method. The paddle apparatus (Apparatus 2; USP) at agitation conditions of 50 rpm, and medium composition of hydrochloric acid (0.1 M) were chosen. The proposed dissolution specification is "Q = (b) (4) at 30 minutes".

In summary, the dissolution method and proposed specification are as follows:

Apparatus:	Paddle (Apparatus 2)
Agitation:	50 rpm
Medium:	900 mL 0.1 M HCl
Temperature:	37°C
Sampling time:	30 minutes

Proposed specification: "Q = (b) (4) at 30 minutes"

The sponsor performed three bioequivalence studies to compare the TBM Linagliptin/metformin FDC tablets and the individual tablets used in the Phase III pivotal efficacy study. These studies are:

1. **Study 1288.1** was conducted to demonstrate bioequivalence between the highest proposed FDC dose strength (L2.5/M1000) and individual linagliptin tablets (2.5 mg) or EU commercial Glucophage® (metformin) tablets (1000 mg). Test and reference products were analyzed by comparative dissolution testing in three different media (pH 1, 4.5, and 6.8) using the proposed dissolution method for linagliptin / metformin hydrochloride film-coated tablets.

2. **Study 1288.2** was conducted to demonstrate bioequivalence between the lowest proposed FDC dose strength (L2.5/M500) and individual linagliptin tablets (2.5 mg) or EU commercial Glucophage® (metformin) tablets (500 mg). Test and reference products were analyzed by comparative dissolution testing in three different media (pH 1, 4.5, and 6.8) using the proposed dissolution method for linagliptin / metformin hydrochloride film-coated tablets.

3. **Study 1218.57** was conducted to demonstrate bioequivalence between Glucophage from Merck and Glucophage from BMS at the dose strength of 500 mg and 1000 mg. Metformin hydrochloride tablets (Glucophage®) sourced from the US and EU market and tested in the bioequivalence study 1218.57 were also compared by dissolution testing.

In addition, the sponsor performed another bioequivalence study (**Study 1288.3**) to compare the to-be-marketed L/M FDC tablets and the individual tablets at the intermediate dose strength of L2.5/M850 in order to demonstrate bioequivalence between the FDC dose strength (L2.5/M850) and individual linagliptin tablets (2.5 mg) or EU commercial Glucophage® (metformin) tablets (850 mg). Additionally, the sponsor performed dissolution testing using the proposed method to demonstrate comparability between US commercial Glucophage® and EU commercial Glucophage®tablets at a dose strength of 850 mg.

Furthermore, the first three production scale batches of each dosage strength (primary stability batches) were compared by *in vitro* dissolution with linagliptin / metformin hydrochloride tablet batches tested in bioequivalence studies 1288.1, 1288.2, and 1288.3.

The manufacturing process of linagliptin / metformin hydrochloride film-coated tablets was developed initially at Boehringer Ingelheim's site in Biberach, Germany, and then transferred to the intended commercial manufacturing site of Boehringer Ingelheim in Ingelheim, Germany. The sponsor stated that the same composition, design and operating principle of equipment and the same general manufacturing process were utilized throughout the pharmaceutical development, including manufacture of the clinical trial supply batches at the Biberach manufacturing site and manufacture of the primary stability batches and further batches for clinical trial supply at the production site in Ingelheim. The production site Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim is the intended commercial manufacturing site. The sponsor submitted comparative dissolution profiles of linagliptin / metformin hydrochloride film-coated tablets manufactured at R&D site Boehringer Ingelheim, Biberach and at manufacturing site Boehringer Ingelheim, Ingelheim.

The biopharmaceutics review will be focused on the proposed dissolution method and specifications.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 201281(0000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. The following comment is to be conveyed to the sponsor at this time:

- FDA request a change to the dissolution specification to no less than (b) (4) of the labeled amount of the drug substance dissolved in 20 minutes.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Lead
Office of New Drugs Quality Assessment

cc: NDA 201-281, MHai, ADorantes, STran, KSharma, AAl-Hakim, SMarkofsky

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOUDA MAHAYNI
03/14/2011

PATRICK J MARROUM
03/14/2011