CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201280Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 201280	Submission Date: 07/02/2010
Brand Name	TBD
Generic Name	Linagliptin
Clinical Pharmacology & Pharmacometric (PM) Reviewer	Lokesh Jain, Ph.D.
Secondary PM Reviewer	Justin Earp, Ph.D.
PM Team Leader	Christine Garnett, Pharm.D.
Clinical Pharmacology Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products
Sponsor/Authorized Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Type; Code	Original NDA 505(b)(1); Standard
Formulation; Strength(s)	IR Tablet ; 5 mg
Indication	To improve glycemic control in patients with type 2 diabetes mellitus

List of Tables

List of Figures

1 Executive Summary

Boehringer Ingelheim Pharmaceuticals, Inc. has submitted NDA 201280 to seek a marketing approval for linagliptin. If approved, it will be the third in DPP-4 inhibitor class to be marketed in the USA. Two of the previous drugs, sitagliptin (Januvia, NDA 21-995) and saxagliptin (Onglyza, NDA 22-350), were approved by the FDA in 2006 and 2009, respectively.

Linagliptin is intended to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). The proposed indication is the use of linagliptin as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM. To support this indication, the sponsor has studied linagliptin as monotherapy and in combination therapy with metformin, sulfonylureas, and pioglitazone. The clinical program presented in this submission includes 24 Phase 1, 4 Phase 2, and 9 Phase 3 clinical trials.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 201280 for linagliptin and finds it acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dose-Response

- Dose-response relationship demonstrated no additional reduction in HbA1c with increase in dose from 5 mg to 10 mg following co-administration with metformin in a 12-week therapy (Trial 1218.6).
- Reduction in HbA1c for 2.5 and 5 mg dose was also comparable after 12-week monotherapy with linagliptin (Trial 1218.5)
- 5 mg dose was more likely to achieve >80% inhibition of DPP-4 at steady-state compared to 2.5 mg dose.

Exposure-Response

- A relationship was established between linagliptin exposure and HbA1c response by using the predicted steady-state exposures for 1 to 10 mg linagliptin doses. Changes in HbA1c from baseline (ΔHbA1c) increased with increasing exposure and reached plateau at exposures greater than approximately 100 nM·h.
- Exposures for 5 mg dose covered the exposure resulting in maximum reduction in HbA1c.

Pharmacodynamics

- The extent of dipeptidyl peptidase-4 (DPP-4) inhibition increased with increases in 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 (Trial 1218.2).
- The concentrations of incretin hormone glucagon-like peptide 1 (GLP-1) increased by about 3-fold for linagliptin doses ranging from 2.5 to 10 mg compared to placebo (Trial 1218.3).

Pharmacokinetics

- Linagliptin followed 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 be explained by concentration dependent binding to 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.
- T_{max} is reached between 0.5 to 3 h
- The accumulation half-life of linagliptin ranged from 8-12 hours.
- Metabolism is a minor pathway of elimination for linagliptin. The majority of drug is eliminated unchanged in feces (~85%) and a minor proportion in urine (~4.5%). Enterohepatic circulation contributes to linagliptin elimination.
- The predominant metabolite, CD1790 (formed by CYP3A4 isoform), is therapeutically inactive.
- Co-administration with high-fat meal reduced linagliptin rate of absorption (i.e., C_{max}) by ~15 to 25% but had no effect on AUC (Figure 1). These changes were not considered clinically relevant.
- According to population PK, the between subject variability on clearance was low (i.e., CV% of 24%). Gamma glutamyl transferase (GGT) was a significant covariate for clearance but had no clinically meaningful effect.

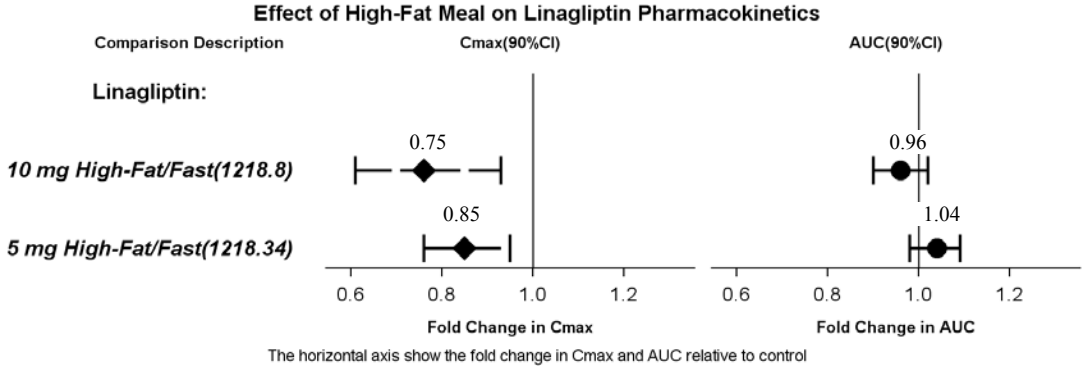


Figure 1: Forest plot demonstrating the effect of high-fat mean on linaglipitn PK

Specific Population

- No dose-adjustments are recommended for subjects with renal or hepatic impairment (Figure 2).

- Age, weight, BMI, and gender had no clinically meaningful effect of linagliptin PK.
- Linagliptin exposures in subjects with Japanese and Chinese ethnicity were ~25-30% higher than that of Caucasian subjects. This small change was not expected to be clinically meaningful.

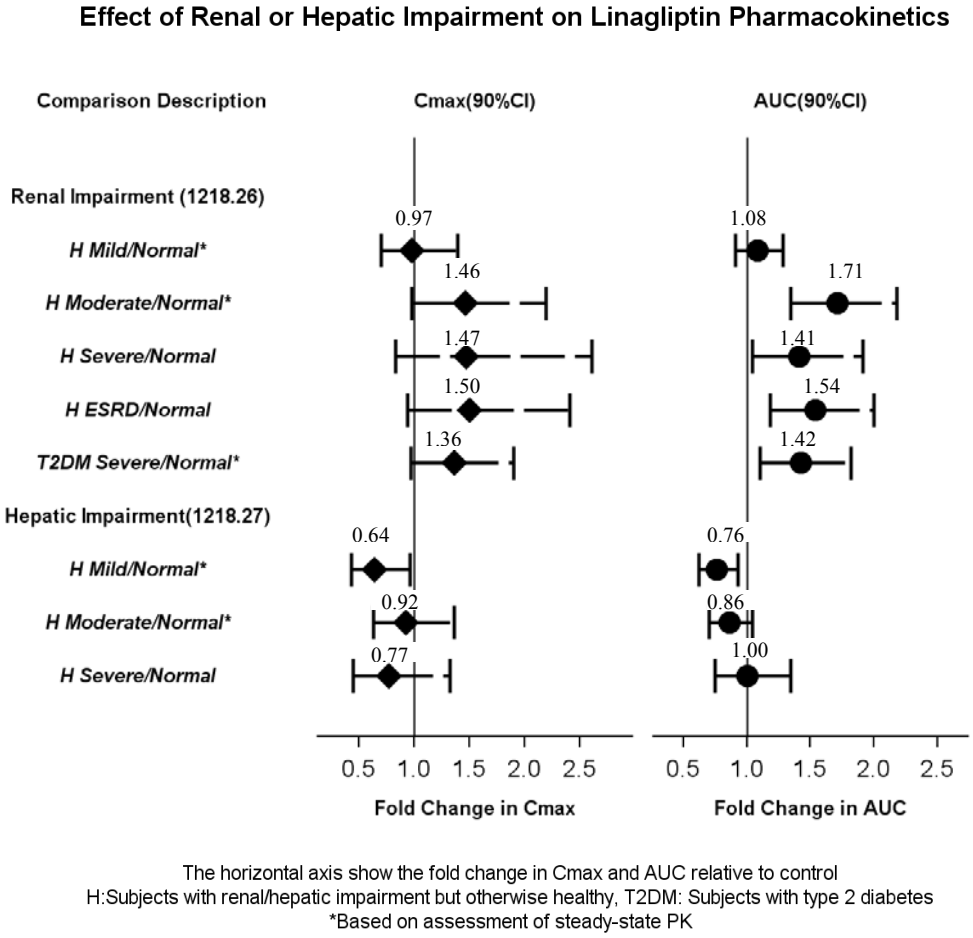


Figure 2: Forest plot demonstrating the effect of renal and hepatic impairment on linagliptin PK

Drug-Drug Interaction (DDI)

- Forest plots showing the geometric means for comparison of AUC and C_{max} based on DDI studies are shown in Figure 3 and Figure 4.
- No dose adjustments of linagliptin are recommended for co-administration with P-gp and CYP 3A4 inhibitors. Two-fold increase of exposure's safety has been tested in a Phase 3 trial with 10 mg, which were found to be safe (C_{trough} for 10 mg dose was 8.07-8.92 nM against C_{trough} for 5 mg dose of approximately 5.0 nM). Please refer to section 2.4.1.6 for details.
- Linagliptin co-administration with P-gp and CYP 3A4 inducers may reduce its efficacy because of lower linagliptin exposures; therefore, it is strongly recommended to use the alternative treatments when it is to be co-

administered with P-gp or CYP 3A4 inducers. Please refer to section 2.4.1.6 for details.

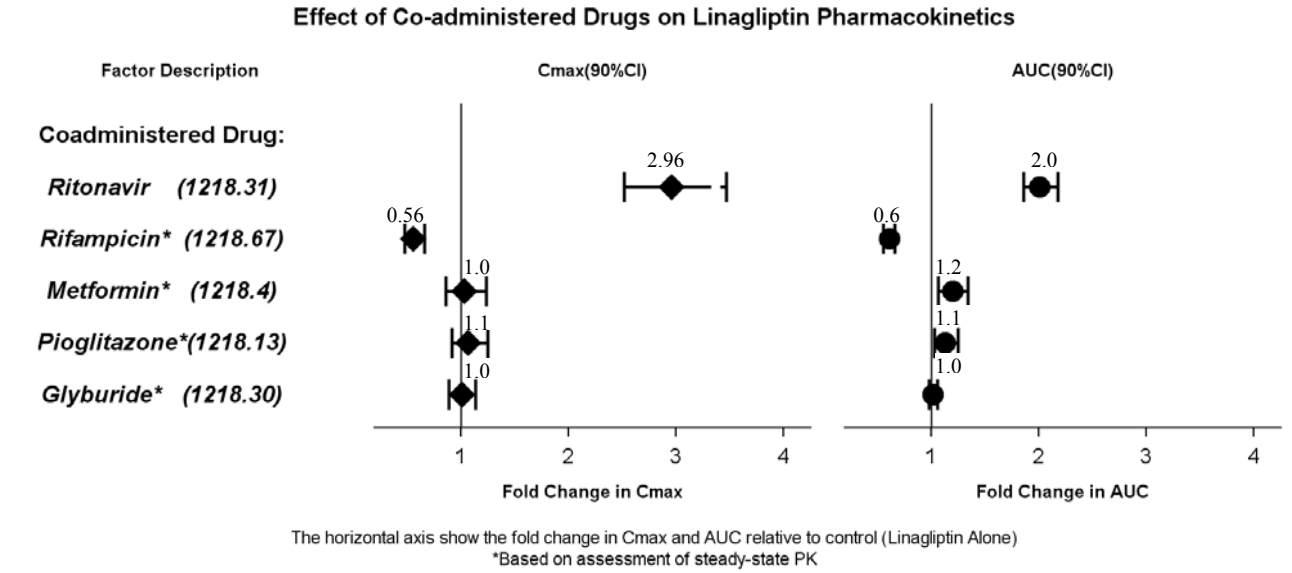


Figure 3: Forest plot demonstrating the effect of co-administered drugs on linagliptin PK

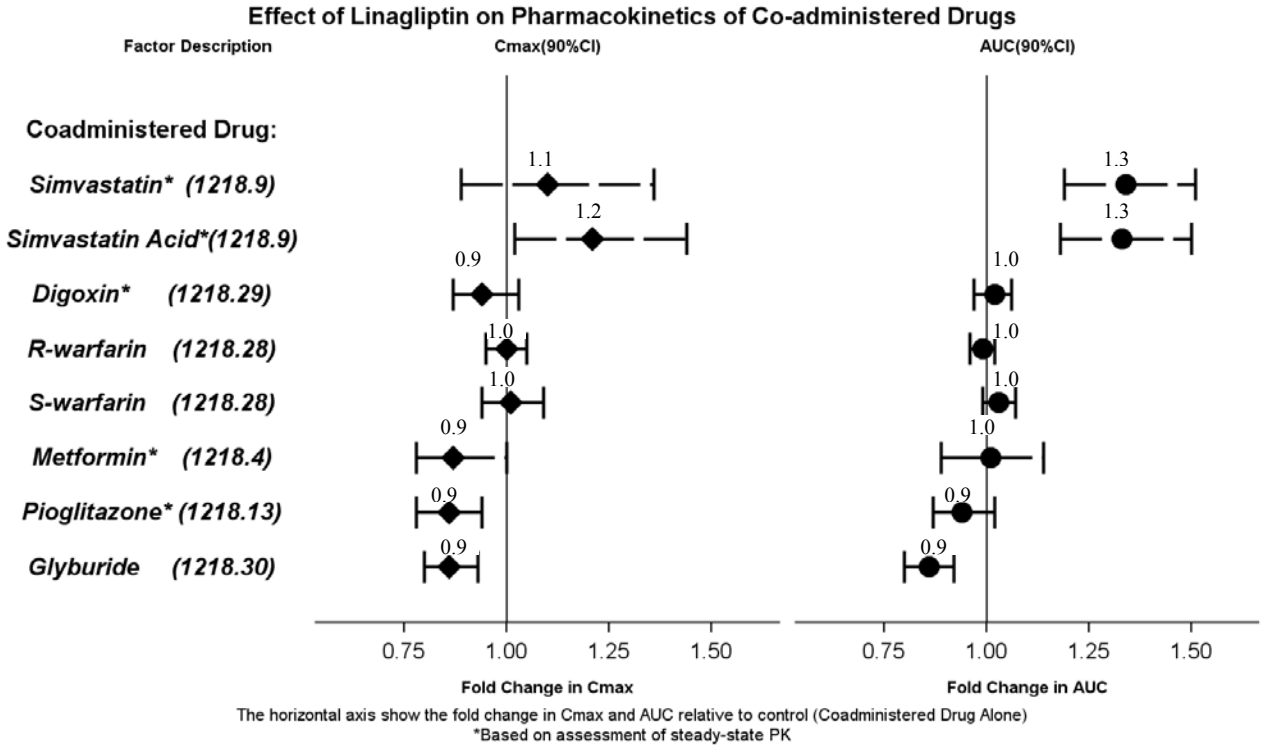


Figure 4: Forest plot demonstrating the effect of linagliptin on PK of co-administered drugs

2 Question-Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Linagliptin is a small molecule drug with one chiral center (denoted with * in Figure 5). The R-enantiomer is used as an active ingredient. The enantiomeric excess of the R-enantiomer accounted for (b) (4) in humans. Physical and chemical properties of linagliptin are displayed in Table 1.

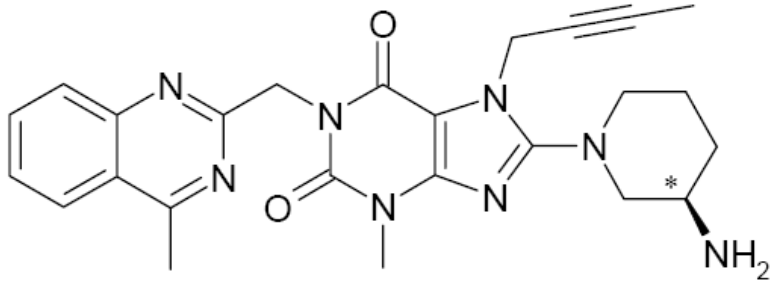


Figure 5: Linagliptin chemical structure

Table 1: Linagliptin physical-chemical properties.

Molecular Formula	$C_{25}H_{28}N_8O_2$
Molecular Weight	472.54 g/mol
Physical State	Powder
Polymorphism	(b) (4)
Dissociation Constants	pK_{a1} = 8.6, protonation of the primary amino group pK_{a2} = 1.9, protonation of the quinazoline moiety
Solubility	• Water: 0.9 mg/mL • >1 mg/mL in aqueous media over entire physiological pH range • Reduces to ~0.6 mg/mL at pH>8
Partition Coefficient	Log P=1.7 of the neutral form (free base) Apparent partition coefficient: log D=0.4 at pH 7.4
Stability	• Very stable in solid state • Relatively stable in aqueous solution at neutral and intrinsic pH and moderately stable in strongly basic pH

Drug Product

Linagliptin is formulated as an immediate release (IR) film coated tablet containing 5 mg of drug and is presented as light red, round, biconvex tablets. The tablets are marked with "D5" on one side and have the Boehringer Ingelheim logo on the other side. This

formulation was different from the formulation tested in Phase 3 clinical trials (b) (4) [redacted] (see section 2.5.2 for more details).

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Linagliptin is an orally administered DPP-4 inhibitor. The inhibition of DPP-4 prolongs the half-life of endogenous incretin hormones, GLP-1 and GIP (glucose dependent insulinotropic polypeptide). Both incretin hormones are involved in physiological regulation of glucose homeostasis. These are gastrointestinal hormones, which stimulate the release of insulin and lower the plasma glucagon levels after consumption of meals (Figure 6). GLP-1 activity ceases when the glucose concentration falls below 55 mg/dL, indicating that prolongation of the half-life of GLP-1 by DPP-4 inhibitors bears little risk of hypoglycaemia. Sponsor reported IC_{50} value for inhibition of DPP-4 by linagliptin is 1 nM.

This NDA applies for the use of linagliptin as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM.

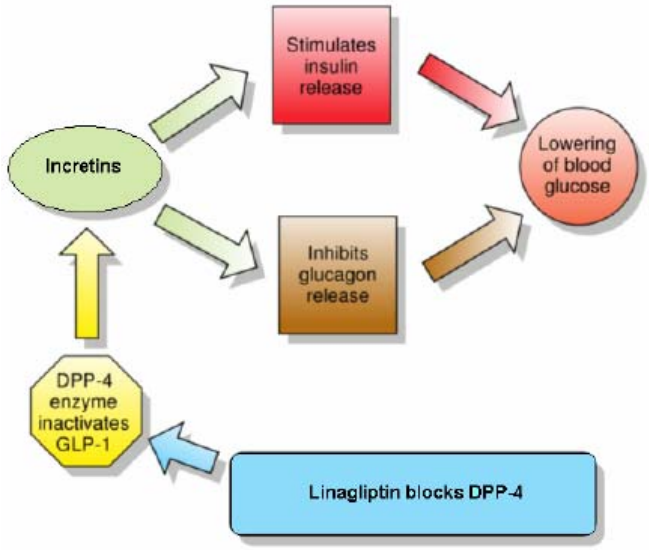


Figure 6: Linagliptin mechanism of action

2.1.3 What are the proposed dosages and routes of administration?

Proposed dose for linagliptin IR tablet is 5 mg, which is to be administered orally.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

Linagliptin clinical pharmacology and clinical development program consisted of the following studies. (N=number of studies)

I. Phase 1 (Healthy Volunteers)

a. Pharmacokinetics (N=5): Single dose, multiple dose, dose proportionality, comparison of bid vs. qd regimen, and mass balance
b. Specific population (N=5): PK in Chinese, PK in Japanese, PK in African-Americans (interim analysis), renal impairment, and hepatic impairment
c. Biopharmaceutics (N=3): Food effect, relative bioavailability and bioequivalence
d. Drug-drug interaction studies (N=9): with ritonavir, rifampicin, metformin, pioglitazone, glyburide, simvastatin, warfarin, digoxin, and oral contraceptive
e. QT study (N=1)

II. Phase 1 (T2DM)
Multiple dose PK (N=2) and renal impairment study included both healthy subjects and patients with T2DM

III. Phase 2
a. Dose finding study (N=3)
b. Clinical trial to assess 4 week pharmacodynamics (N=1)

IV. Phase 3 (N=9)
a. Pivotal double-blind placebo controlled studies with a treatment duration of 24 weeks (studies 1218.15, 1218.16, 1218.17, and 1218.18)
b. A double-blind active-controlled trial (study 1218.20)
c. Double-blind placebo-controlled trials of 18 weeks treatment duration (studies 1218.35 and 1218.50)
d. Placebo- and active-controlled study of 52 weeks with an extension for safety evaluation (study 1218.23)
e. An open-label extension study (study 1218.40)

V. Population pharmacokinetic analysis – was performed using data from two Phase 2 trials (1218.5 and 1218.6) and two Phase 1 trials (1218.2 and 1218.3)

2.2.2 What are the evidences of efficacy provided by the sponsor in support of the proposed 5 mg dose?

Sponsor proposes to market the 5 mg strength for linagliptin, effectiveness of which was evaluated in Phase 2 and Phase 3 clinical trials. This is the only dose that was tested in all Phase 3 efficacy trials except one Phase 3 trial in Japanese patients (Trial 1218.23), which also tested an additional dose of 10 mg. Phase 2 trials evaluated doses ranging from 0.5 to 10 mg. Selection of 5 mg dose was based on evidence of effectiveness for DPP-4 inhibition (%) and change in HbA1c from baseline, which are described below.

Effect of linagliptin on DPP-4 inhibition

Linagliptin acts by inhibiting the DPP-4, which occurs in a dose dependent manner. The extent of DPP-4 inhibition for rising doses from 1 mg to 10 mg was measured in a multiple rising dose study 1218.2 of 12 days duration. Results from this study are shown in Figure 7. The geometric mean (%CV) of minimum plasma DPP-4 activity (E_{min} and $E_{min,ss}$) and the plasma DPP-4 activity 24 hours after dosing (E_{24} and $E_{\tau,ss}$) on days 1 and 12 are summarized in Table 2. Average DPP-4 inhibitions at 24 hours after the last dose (i.e., at steady-state) were 62.5%, 76.9%, 85%, and 89.4% for 1 mg, 2.5 mg, 5 mg, and 10 mg dosing groups, respectively. The pre-specified criterion for selection of a fully

effective dose was >80% DPP-4 inhibition at trough or steady state in >80% of patients, which was met with the 5 and 10 mg doses (Figure 7). Similar results were obtained in a 12-week trial 1218.6, in which linagliptin was co-administered with metformin (see individual study reports, Table 54) and DPP-4 inhibition of >80% in more than 80% of patients at steady-state (week 12) was achieved for 5 and 10 mg dose. Results from all other trials which evaluated the DPP-4 inhibition at trough are summarized in Table 55 in individual study reports.

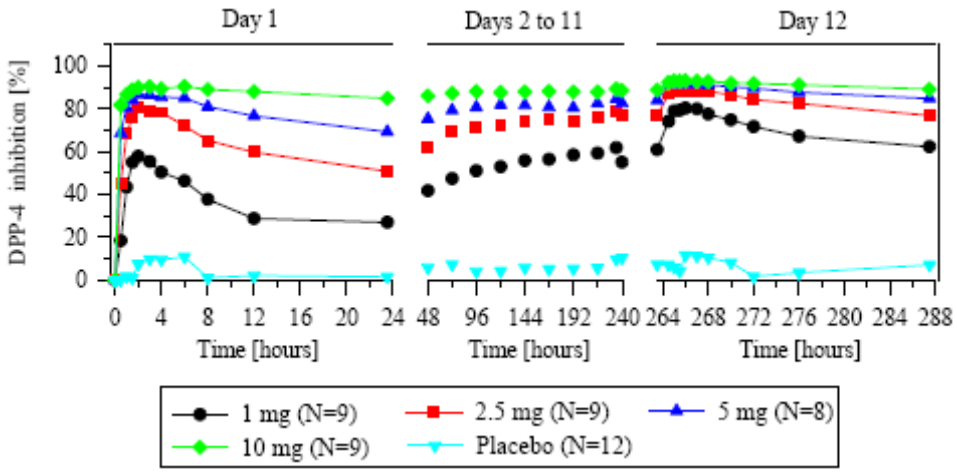


Figure 7: DPP-4 inhibition from baseline induced by linagliptin in the multiple rising dose Phase 1 study 1218.2

Table 2: Geometric mean (%gCV) DPP-IV activity on days 1 and 12 after oral administration of 1, 2.5, 5 and 10 mg linagliptin once daily for 12 days in study 1218.2

Dose	E_{min} [%]	E_{24} [%]	$E_{min,ss}$ [%]	$E_{\tau,ss}$ [%]
Placebo	86.9 (10.6)	98.1 (9.00)	81.1 (14.1)	91.9 (15.2)
1 mg	36.5 (46.7)	72.5 (13.8)	17.7 (28.6)	37.5 (13.6)
2.5 mg	16.9 (30.1)	48.4 (19.1)	10.5 (19.4)	23.1 (12.6)
5 mg	10.8 (43.8)	29.1 (35.9)	7.69 (13.9)	15.0 (19.5)
10 mg	8.32 (24.8)	14.7 (27.9)	6.33 (19.9)	10.6 (24.6)

Effect of linagliptin on HbA1c

Change in %HbA1c was the primary marker of efficacy for all linagliptin trials. The results from its assessment in Phase 2 and Phase 3 clinical trials are as follows:

Phase 2 trial – 1218.6 (Linagliptin in background of metformin therapy)

Trial 1218.6 tested efficacy of linagliptin in combination with metformin for 12-week duration in patients with T2DM. A statistically significant effect was observed for all tested doses of 1 mg, 5 mg, and 10 mg, which resulted in a 0.4%, 0.8%, and 0.7% placebo-corrected reduction in HbA1c, respectively (Figure 8). These results demonstrate that 1 mg dose was sub-therapeutic and there was no added benefit for 10 mg dose

compared to the 5 mg dose. Please refer to Figure 18 in individual study report for change in HbA1c across time.

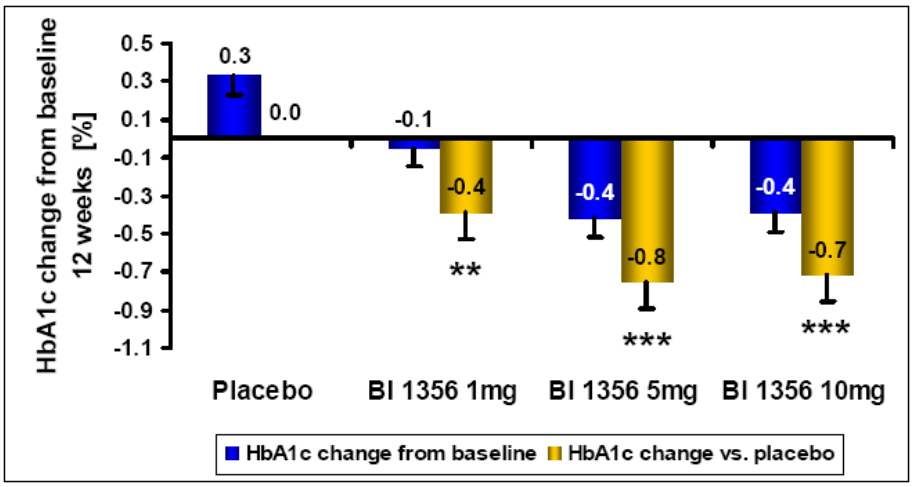


Figure 8: Adjusted mean (SE) for HbA1c change from baseline and change versus placebo after linagliptin (BI 1356) oral administration in the add-on to metformin Phase 2 study 1218.6. **p<0.01, ***p<0.001

Phase 2 trial – 1218.5 (Linagliptin monotherapy)

Trial 1218.5 evaluated linagliptin as monotherapy for 12-week duration in patients with T2DM. Doses of 2.5 mg and 5 mg of linagliptin resulted in a significant placebo corrected HbA1c reduction of up to 0.46% (Figure 9). The reduction in HbA1c for 2.5 and 5 mg dose appeared to be similar, and 0.5 mg dose was less effective than both of them. In this trial metformin in daily dose of 1000 mg twice-a-day was tested as an active comparator, which resulted in 0.9% placebo-corrected reduction in HbA1c at week 12 (data not shown in Figure 9). Please refer to Figure 17 in individual study report for change in HbA1c across time.

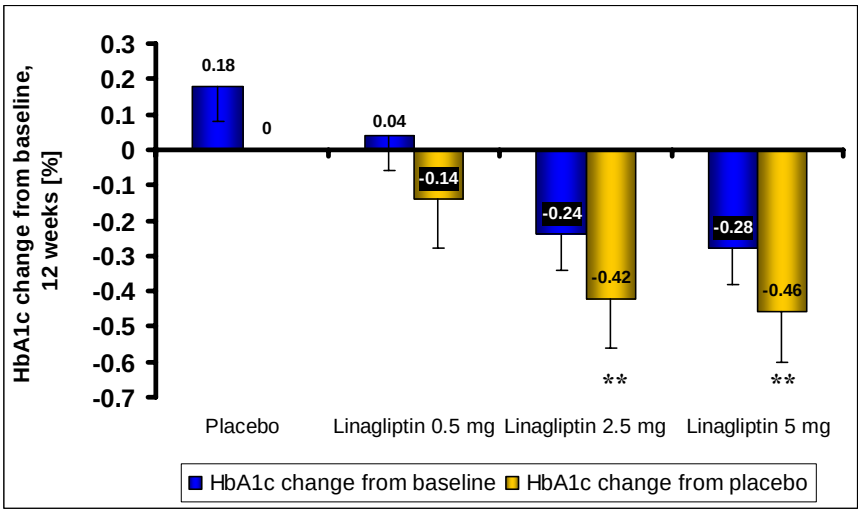


Figure 9: Adjusted means (SE) for HbA1c change from baseline and HbA1c change versus placebo after oral administration of linagliptin or placebo in monotherapy for 12 weeks in Phase 2 study 1218.5. **p<0.01

Phase 3 trial – 1218.23 (active controlled trial)

Phase 3 trial 1218.23 in Japanese patients evaluated linagliptin at dose levels of 5 mg and 10 mg against placebo arm and an active comparator arm administering voglibose (a product available in Japan for prevention of type 2 diabetes). Although the total trial duration was 52 weeks (26 weeks double blind Phase followed by 26 weeks of open label extension), the superiority against placebo was tested only in first 12 weeks of double blind phase. Adjusted mean change from baseline in HbA1c at week 12 was -0.25% for both linagliptin doses of 5 mg and 10 mg compared to 0.63% for placebo (Figure 10). The placebo-adjusted mean (95% CI) change in HbA1c from baseline at week 12 was -0.88% (-1.05, -0.70) for both treatment arms (Figure 10). There was no additional reduction in HbA1c for increase in dose from 5 to 10 mg.

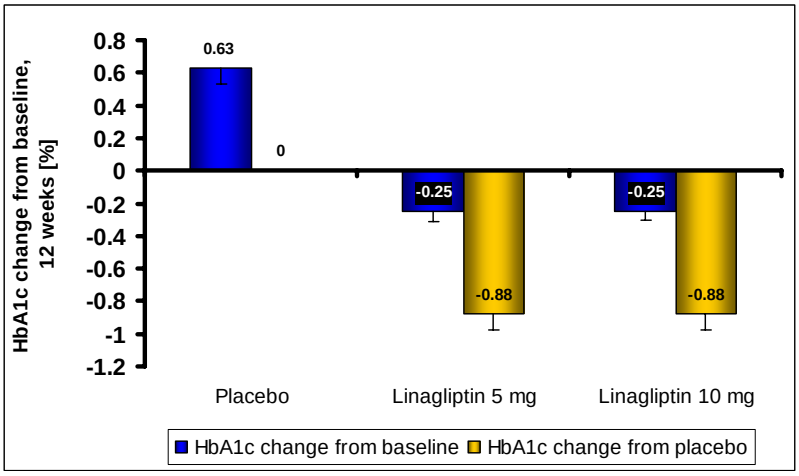


Figure 10: Adjusted means (SE) for HbA1c change from baseline and HbA1c change versus placebo after oral administration of linagliptin or placebo in monotherapy for 12 weeks in Phase 3 study 1218.23

Effect of linagliptin on GLP-1 concentrations

Inhibition of DPP-4 by linagliptin prolongs the half-life of GLP-1; therefore, mechanistically GLP-1 levels are expected to rise after treatment with linagliptin. In a 4-week Phase 1 trial (Trial # 1218.3) in patients with T2DM, GLP-1 levels were measured to determine the impact of DPP-4 inhibition on GLP-1 concentrations. Blood samples for GLP-1 were collected 30 min after beginning of a meal tolerance test (MTT) on day -1 and day 29 (24h after the last study drug intake). GLP-1 levels were found to be highly variable and about one third of samples were below the detection limit. There was up to 3 fold increase in plasma GLP-1 levels for the 2.5, 5, and 10 mg doses in the 4-week treatment duration (Figure 11). However, due to the high variability and the low sample size, these changes were not statistically significant.

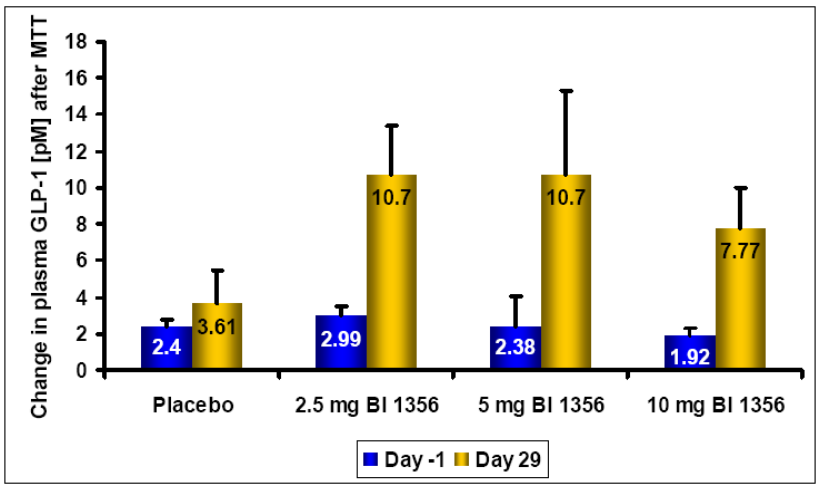


Figure 11: Arithmetic mean (standard error SE) difference of GLP-1 plasma concentrations measured before and 30 min after an MTT on days -1 and 29 (24h after last study drug intake) after multiple administration of linagliptin or placebo for 28 days in the Phase I study 1218.3

Effect of linagliptin on glucose levels

In a 12-days multiple rising dose Phase 1 trial 1218.2, AUC glucose concentrations after an oral glucose tolerance test (oGTT) were measured at baseline and on day 13 (24 hours after the last dose) (Figure 12). The $AUC_{0\text{-}2h,\ Glucose}$ for 2.5 mg, 5 mg, and 10 mg dose were significantly less compared to baseline and compared to placebo.

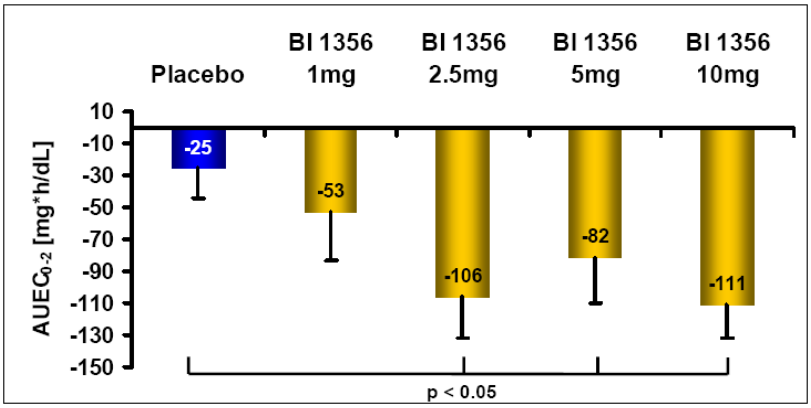


Figure 12: Arithmetic mean (SE) change from baseline of glucose $AUEC_{0\text{-}2h}$ after an oGTT at steady state (day 13, 24h after the last study drug intake) after oral administration of 1 mg, 2.5 mg, 5 mg or 10 mg linagliptin or placebo for 12 days in the multiple rising dose Phase 1 study 1218.2

Summary

In summary, as per the sponsor the 5 mg dose met both of their criteria of dose selection in most of the trials: (a) DPP-4 inhibition of >80% in more than 80% of patients at steady-state and (b) optimal reduction in HbA1c. In none of the trials with 2.5 mg dose DPP-4 inhibition reached 80% at steady-state, while 10 mg dose had no greater reduction in HbA1c than the 5 mg dose. Additionally, increase in GLP-1 concentrations and reduction in glucose $AUC_{0\text{-}2h,\ Glucose}$ for oGTT was observed for all tested linagliptin doses compared to placebo.

Reviewer's comments
This reviewer agrees with sponsor's selection of 5 mg dose given that safety profile of linagliptin has been established for up to 600 mg dose in single-dose study and up to 10 mg dose in multiple-dose study. However, only HbA1c is an established marker of efficacy for anti-diabetic drugs and the clinical relevance of 80% criteria for DPP-4 inhibition is not yet completely known. Since both 2.5 mg and 5 mg dose had almost similar reduction in HbA1c, sponsor could have also further evaluated the 2.5 mg dose.

2.2.3 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Sponsor has used HbA1c as the primary endpoint for all key efficacy studies. Use of HbA1c as an indicator of glycemic control is widely accepted and is also recommended by the American Diabetes Association (ADA) and in FDA's diabetes mellitus drug development guidance for industry. In addition several other pharmacodynamic markers based on mechanism of action were used in clinical pharmacology or efficacy clinical trials such as glucose, insulin, pro-insulin, C-peptide, fructosamine, 1, 5-anhydroglucitol, DPP-4 activity, DPP-4 concentrations, active GLP-1, glucagon, and histamine.

2.2.4 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, please refer to analytical section.

2.2.5 What are the characteristics of the dose-response and exposure-response relationships for efficacy?

Dose-response relationship for linagliptin
The dose-response relationship for change in primary efficacy marker (i.e., %HbA1c) and other pharmacodynamic markers from these trials are discussed under question 2.2.2 and are shown in Figures 7 to 12. These results are also summarized in Table 3.

In brief, change in HbA1c from baseline increased for doses 0.5 to 2.5 mg, remained almost similar for 2.5 and 5 mg dose, and there was no additional reduction seen for 10 mg dose compared to the 5 mg dose. The DPP-4 inhibition increased from 1 to 10 mg, and more than 80% inhibition at steady-state was achieved with both 5 mg and 10 mg dose.

The reduction in fasting plasma glucose also increased from 0.5 mg to 2.5 mg (Table 3), and was comparable between 5 mg and 10 mg dose. On an average response for both 5 mg and 10 mg was higher than the response for 2.5 mg. These results suggest no additional advantage of increasing the dose from 5 mg to 10 mg. However, in study 1218.5, the reduction in fasting plasma glucose for 2.5 mg dose was higher than the 5 mg dose (Table 3).

In summary, both primary and secondary efficacy endpoints improved with increase in dose, and reached a maximum response at doses of 5 mg and 10 mg. Please refer to clinical review for efficacy information for 5 mg linagliptin dose in Phase 3 trials.

Table 3: Change in efficacy endpoints or pharmacodynamic markers at week 12 for clinical trials supporting the selection of 5 mg dose

Parameter	1218.5*			1218.6†			1218.23‡	
	0.5mg	2.5mg	5mg	1mg	5mg	10mg	5mg	10mg
DPP-4								
Mean DPP-4 inhibition (%)	40.5	65.5	65.7	57.6	82.2	86.3	79.5	86.2
Median DPP-4 inhibition (%)	38.5	74.5	81.0	63.0	85.0	90.0	81.5	88.0
% of patients with >80% DPP-4 inhibition at trough	0	27.1	55.1	8	87	93	59.1	90.3
HbA1c								
Change from baseline (%)	0.04	-0.24	-0.28	-0.16	-0.48	-0.42	-0.24	-0.25
Placebo-corrected change(%)	-0.14	-0.42	-0.46	-0.40	-0.72	-0.67	-0.88	-0.88
FPG (mg/dL)								
Adjusted mean Change from baseline	6.7	-15.2	-9.1	-6.40	-22.12	-16.26	-12.3	-13.0
Placebo-corrected change	2.5	-19.4	-13.3	-19.0	-34.7	-29.0	-19.7	-20.4

*Trial 1218.5 administered linagliptin as monotherapy
†Trial 1218.6 administered linagliptin with metformin
‡1218.23 was conducted in Japanese patients with T2DM

Exposure-response (ΔHbA1c) relationship for linagliptin

Two linagliptin dose-ranging Phase 2 trials 1218.5 and 1218.6 were used to assess the exposure-response relationship. In these trials HbA1c levels were measured but only trough PK samples were collected. However, these data were included in the population PK analysis and estimates of PK parameters (e.g., CL, V) were determined for each patient.

Steady-state exposures ($AUC_{\tau,ss}$) for these patients were simulated using the sponsor's population PK model (see pharmacometrics review for more details). These simulated $AUC_{\tau,ss}$ data were pooled together to calculate the exposure quartiles. For each quartile of linagliptin $AUC_{\tau,ss}$, the mean change in HbA1c from baseline at week 12 (post-treatment administration) was calculated. These values were plotted to assess the exposure-response relationship as shown in Figure 13. The HbA1c change at 12^{th} week was considered suitable because most of the HbA1c lowering effect of linagliptin occurred between baseline and week 8 with lesser change between week 8 and week 12 (refer to Figures 17 and 18 in individual study reports).

Change in HbA1c from baseline (ΔHbA1c) increased with increasing exposure and reached a plateau at exposures greater than approximately 100 nM*h. Also shown in Figure 13 are the ranges of simulated exposures for dose levels 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg, and 10 mg. Overlap in the ranges of simulated exposures for different dose levels was likely because of non-linear PK. As a result, the exposure quartiles in exposure-response relationship do not exclusively represent only one dose level. Therefore, it is not possible to relate the exposure-response relationship with dose of linagliptin. Nevertheless, the simulated exposure for 5 mg dose overlaps with the exposure quartiles resulting in maximum reduction in HbA1c.

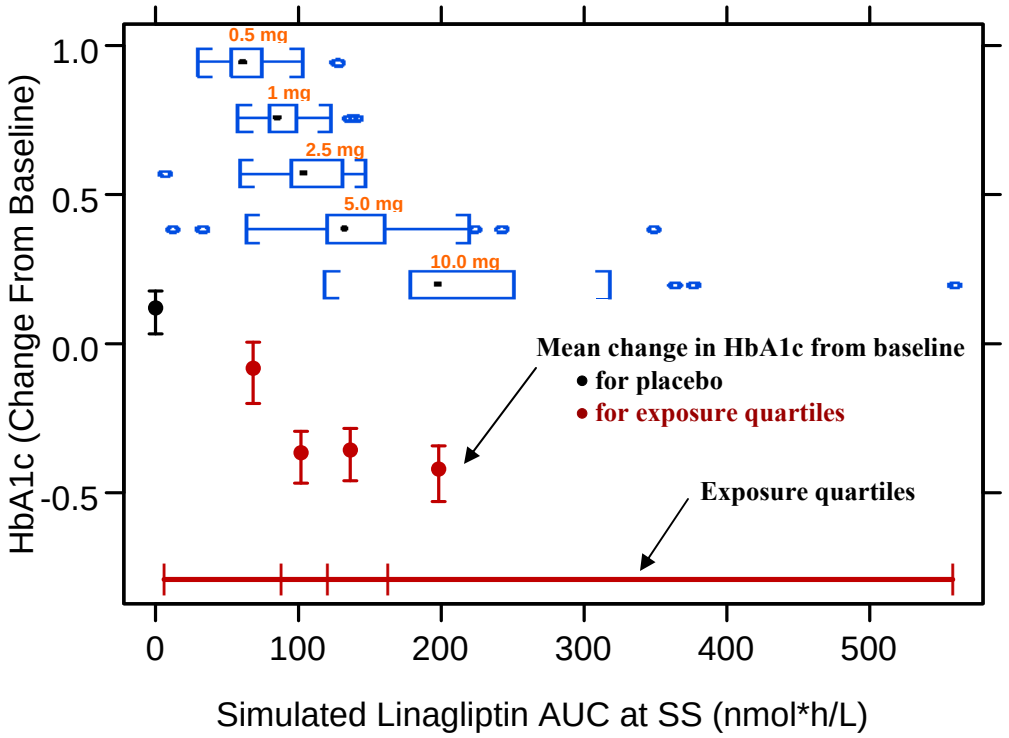


Figure 13: Exposure-Response Relationship Based on Simulated Exposures for Phase 2 trials 1218.5 & 1218.6

2.2.6 What are the characteristics of the dose-response and exposure-response relationships for safety?

The pooled safety data from Phase 2 (1218.5 and 1218.6) and Phase 3 trials (1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, and 1218.50) was analyzed to determine the % incidence of adverse events across dose-levels and across study duration. Some of the adverse events for which we observe an increase in % incidence based on dose and study duration are shown in

Figure 14. The adverse events with incidence rate of ~10% for 5 mg dose were arthralgia and back pain. The incidence of back pain appeared to increase in a dose dependent manner (from ~10% to ~20% for increase in dose from 5 mg to 10 mg). Few other adverse events (

Figure 14) showed a tendency of dose dependent increase in incidence rate (e.g., bronchitis and cataract), but their overall rate was less than 5%. Please refer to clinical review for detailed safety analysis of data from Phase 3 clinical trials.

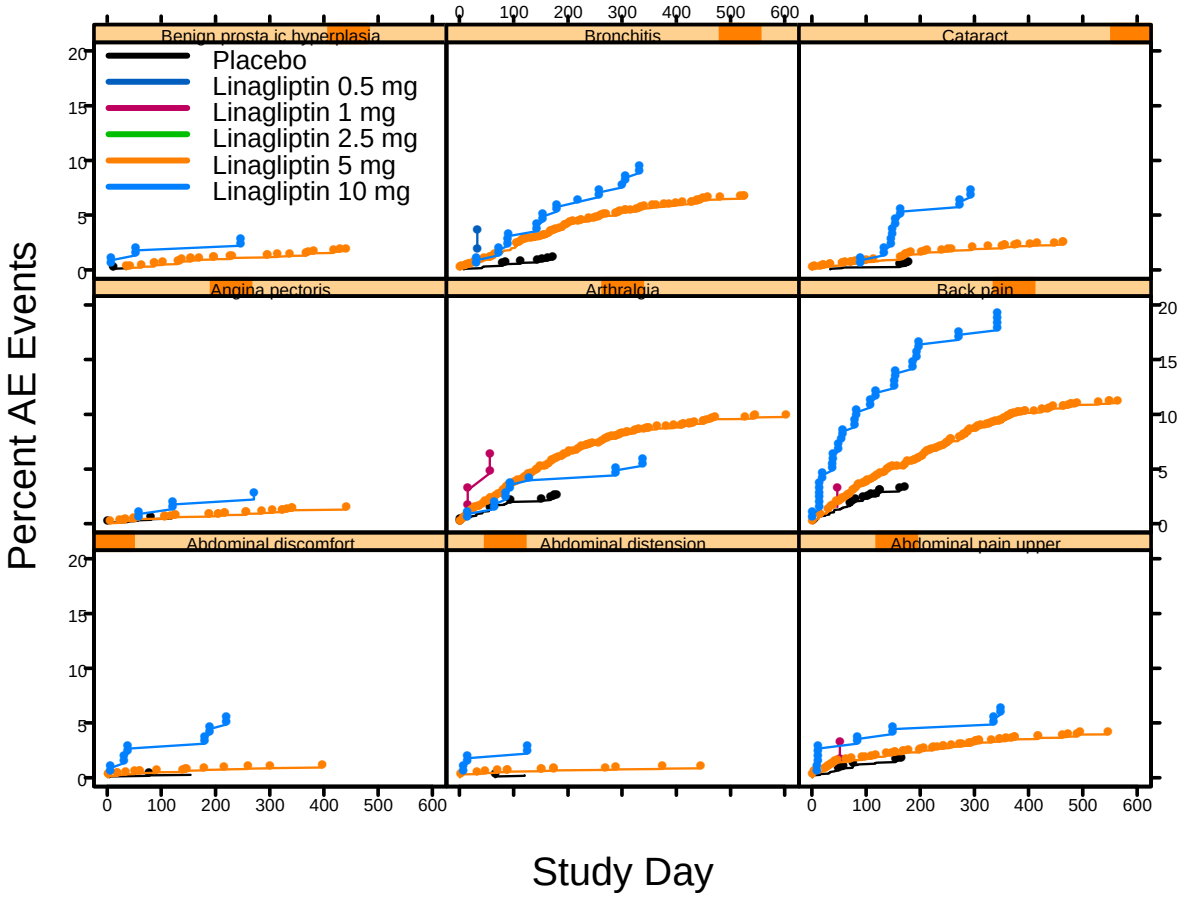


Figure 14: % incidence of selected adverse events across time and across dose based on analysis of pooled safety data from Phase 2 and Phase 3 clinical trials

2.2.7 What are the PK characteristics of the drug?

Linagliptin shows non-linear pharmacokinetics, both after oral and intravenous administration, with a less than dose proportional increase in plasma concentrations in the dose range of 1 mg to 10 mg, which includes the therapeutic dose of 5 mg. The broad overview of linagliptin's disposition profile in humans is presented in Figure 15 and details are presented in the following sub-sections.

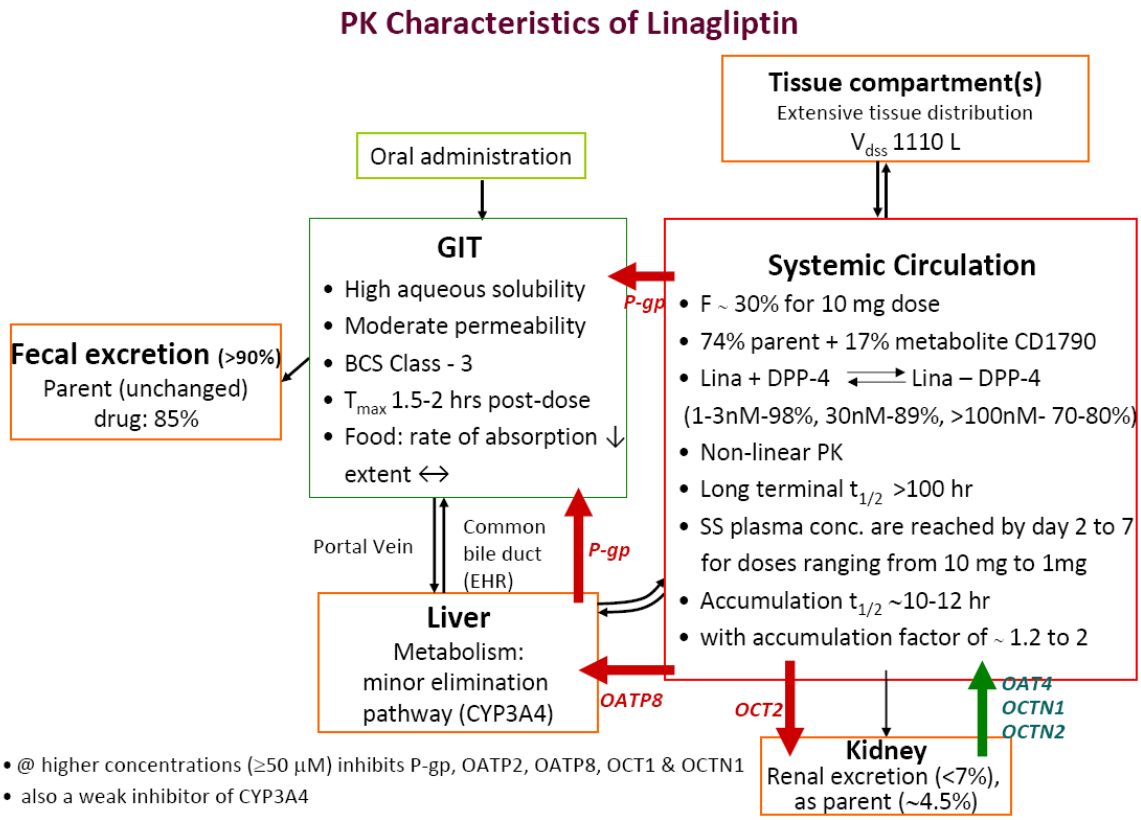


Figure 15: ADME of linagliptin

2.2.7.1 What are the single and multiple dose PK parameters?

Single dose PK (healthy volunteers)

Pharmacokinetics of linagliptin in healthy volunteers has been characterized for both oral administration (Trial 1218.1) and intravenous administration (Trial 1218.10).

Phase 1 study 1218.1

Single dose PK following oral administration of linagliptin was evaluated in the dose range of 2.5 to 600 mg. The plasma concentration-time profiles for these dose levels are shown in Figure 16. Linagliptin followed biexponential disposition kinetics. The peak plasma concentrations of linagliptin are reached between 0.75 to 3 hours. For doses 25 mg and above, two absorption peaks were observed in most subjects, the first between approximately 0.75-2 hours and the second occurred between 3-6 hours. Concentrations declined to about one-tenth of maximum concentrations within 24 hours after administration. The decline in plasma concentrations was steeper for the higher doses, indicating nonlinear distribution and/or elimination processes. Beyond 96 h, plasma concentrations declined in parallel, such that the terminal phase was comparable for all dose groups in the dose range of 2.5 to 600 mg.

The pharmacokinetic parameters for these dose levels are listed in Table 4. The values of $AUC_{0-\infty}$ increased in a less than proportional manner for doses between 2.5 mg and 25 mg, and an almost statistically proportional behavior was observed for doses between 100 mg and 600 mg. Long terminal half lives ranging between 69.7 hours to 79.9 hours were

observed for doses between 2.5 mg and 50 mg and between 128 hours and 184 hours for doses between 100 and 600 mg. However, note that the PK sampling duration for all dose levels were not uniform. Samples were taken up to 120 hour for dose groups 2.5 mg to 50 mg, and it was extended to 192 hour for all other dose groups. Linagliptin showed a large apparent volume of distribution of 2100 L to 2490 L in the dose range of 2.5 mg to 5 mg and 5490 L to 10700 L for doses between 25 and 600 mg. These variations in half-life, apparent clearance, and apparent volume of distribution across dose levels suggest non-linearity. Fractional renal excretion was also dose dependent, and increased from being not measurable for the 2.5 mg dose (i.e., 0%) to 32.7% for the 600 mg dose. This is possibly because of increase in concentration of unbound drug with increase in dose. Nevertheless, at doses between 1 mg to 10 mg renal elimination appears to play a minor role in overall renal disposition. The non-linearity may also explain the observed shape of the plasma concentration-time profiles. At higher concentrations linagliptin will be excreted renally leading to faster decline, whereas renal clearance would become negligible in the terminal phase due to low plasma concentrations, thus resulting in comparable half-lives.

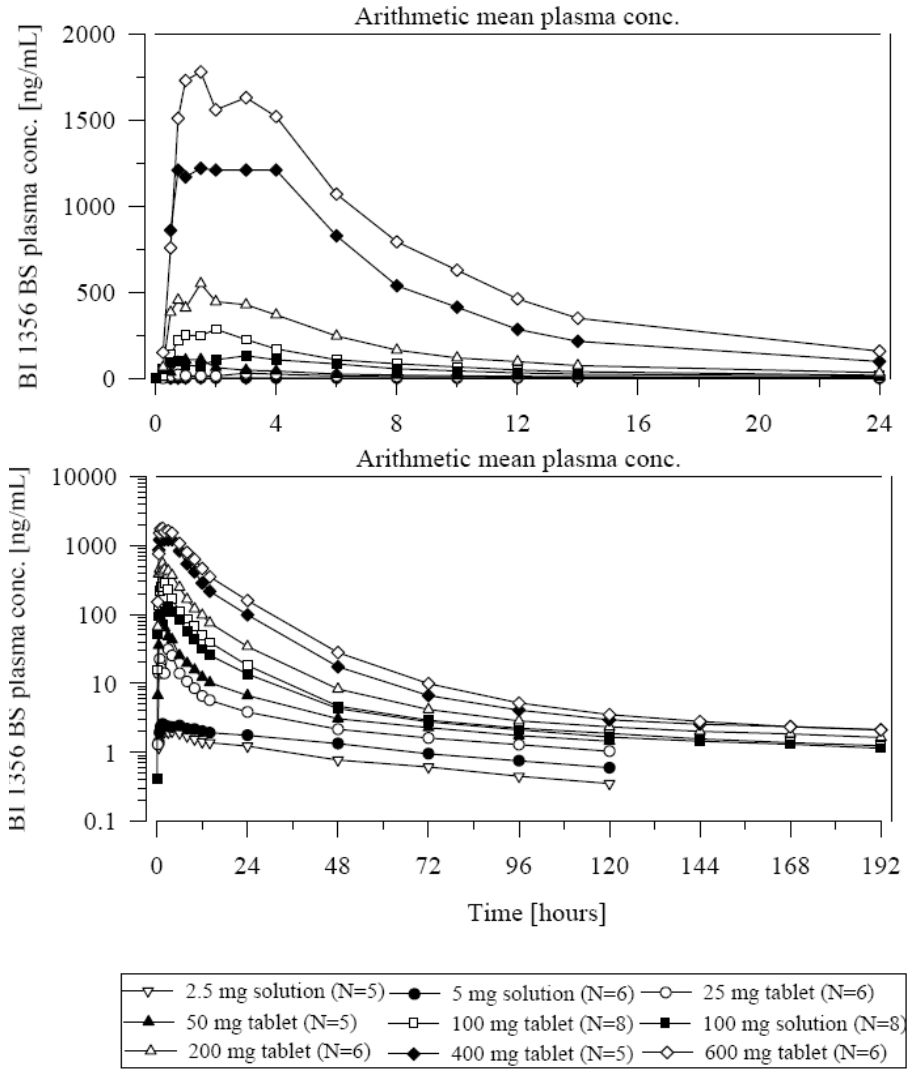


Figure 16: Arithmetic mean drug plasma concentration-time profiles of linagliptin (BI 1356) after single oral administration of 2.5 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 600 mg

linagliptin (upper panel: linear scale, time axis reduced to the first 24 h after drug administration; lower panel semi-logarithmic scale)

Table 4: Key pharmacokinetic parameters of linagliptin after single oral administration of 2.5 to 600 mg dose

Dose (mg)	N	T_{max} (hour) Median (range)	gMean (gCV%)*					
			C_{max} (nM)	$AUC_{0-\infty}$ (nM.hr)	$t_{1/2}$ (hour)	CL/F (mL/min)	V/F (L)	fe_{0-tz} † (%)
2.5 PIB£	5	2.1 (1.5-3.1)	4.4 (19)	290 (34)	79.9 (35)	303 (34)	2100 (13)	NC
5 PIB	6	1.5 (1.0-6.0)	5.7 (19)	427 (33)	69.7 (17)	413 (33)	2490 (27)	0.96 (70)
25 tab€	6	3.0 (0.7-4.0)	72.4 (40)	1110 (16)	79.9 (25)	794 (16)	5490 (38)	6.8 (49)
50 tab	5	0.7 (0.5-1.5)	250 (47)	1930 (26)	75.9 (6)	912 (26)	5990 (27)	9.4 (44)
100 tab	8	1.7 (0.5-3.0)	758 (39)	5690 (21)	143 (20)	620 (21)	7670 (18)	18.2 (26)
100 PIB	8	2.5 (0.5-6.0)	311 (58)	3770 (29)	132 (29)	938 (29)	10700 (45)	13.2 (48)
200 tab	6	1.1 (0.5-2.0)	1440 (26)	10700 (17)	172 (43)	659 (17)	9830 (52)	21.1 (23)
400 tab	5	3.0 (0.7-4.0)	3280 (37)	27700 (36)	184 (51)	509 (36)	8090 (45)	30.4 (20)
600 tab	6	2.2 (0.7-3.0)	4340 (32)	39600 (20)	128 (41)	535 (20)	5920 (58)	32.7 (13)

*gMean= geometric mean, *gCV%=geometric CV%, † fe_{0-tz}=fraction eliminated renally
£PIB=powder-in-bottle formulation, €tab=tablet formulation

Phase 1 study 1218.10

Single-dose PK following 90 minute IV infusion of linagliptin was evaluated in the dose range of 0.5 to 10 mg. In this study 10 mg dose was also administered by oral route for bioavailability assessment. The plasma concentration-time profiles for linagliptin are shown in Figure 17. Linagliptin followed bioexponential disposition kinetics with parallel terminal slopes. The linagliptin pharmacokinetic parameters from this study are summarized in Table 5. IV pharmacokinetic data also show non-linearity up to the maximum tested dose of 10 mg. Both C_{max} and $AUC_{0-\infty}$ increased in a less than dose proportional manner with increase in dose. Clearance and volume of distribution increased with increase in dose. Sponsor used compartmental modeling approach to determine the absolute bioavailability (see pharmacometrics review for model details), which was estimated as 29.5% (inter-individual variability [gCV%] of 46.7) with individual estimates ranging from 12.9% to 60.8% for 10 mg dose.

In addition to linagliptin, this study also measured the main metabolite CD1790. The formation of metabolite was fast as the maximum CD1790 concentrations were already observed within 10 to 90 minutes after the end of the infusion (Figure 18). CD1790 also showed a biphasic disposition profile and had a relatively short half-life of ~12-15 hrs (Figure 18).

Table 5: Key pharmacokinetic parameters of linagliptin after single intravenous infusion or oral administration of 0.5 mg and 10 mg doses

Dose† (mg)	N	T_{max} (hour) Median (range)	gMean (gCV%)*				
			C_{max} (nM)	$AUC_{0-\infty}$ (nM.hr)	$t_{1/2}$ (hour)	CL£ (mL/min)	V_z€ (L)
0.5 iv	6	1.50 (1.50-1.53)	11.7 (19)	422 (25)	126 (21)	41.8 (25)	456 (19)
2.5 iv	6	1.50 (1.50-1.53)	48.6 (24)	821 (26)	139 (19)	107 (26)	1300 (18)
5 iv	10	1.50 (1.50-1.53)	90.9 (15)	1250 (18)	127 (19)	141 (18)	1550 (15)
10 iv	6	1.25 (1.00-1.53)	176.0 (23)	1480 (7)	127 (11)	239 (6)	2620 (11)
10 po	10	3.00 (0.50-4.00)	21.0 (73)	1010 (32)	116 (18)	349 (32)	3520 (27)

[†]iv=intravenous infusion and po=oral administration, *gMean= geometric mean and gCV%=geometric CV%,[£]CL/F for oral administration, [€]V_z/F for oral administration

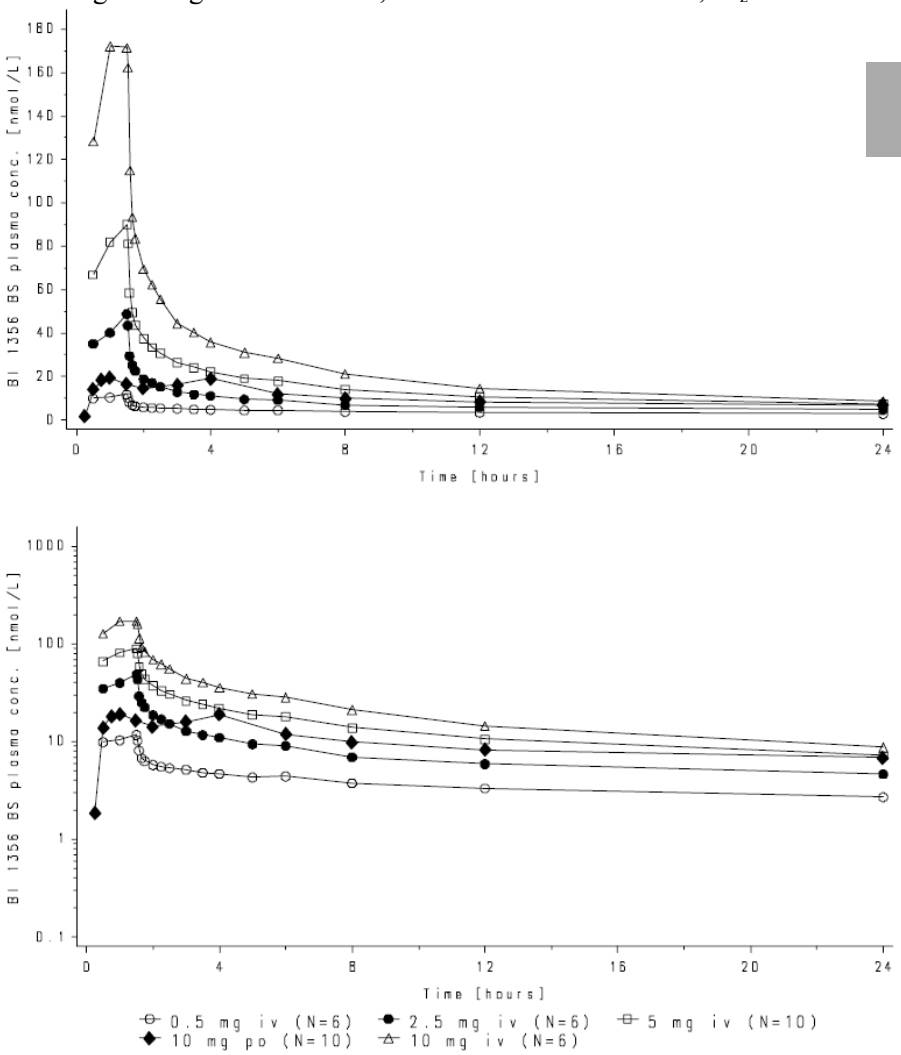


Figure 17: Arithmetic mean plasma concentration-time profiles of linagliptin after intravenous infusion of 0.5-10 mg and oral administration of 10 mg linagliptin

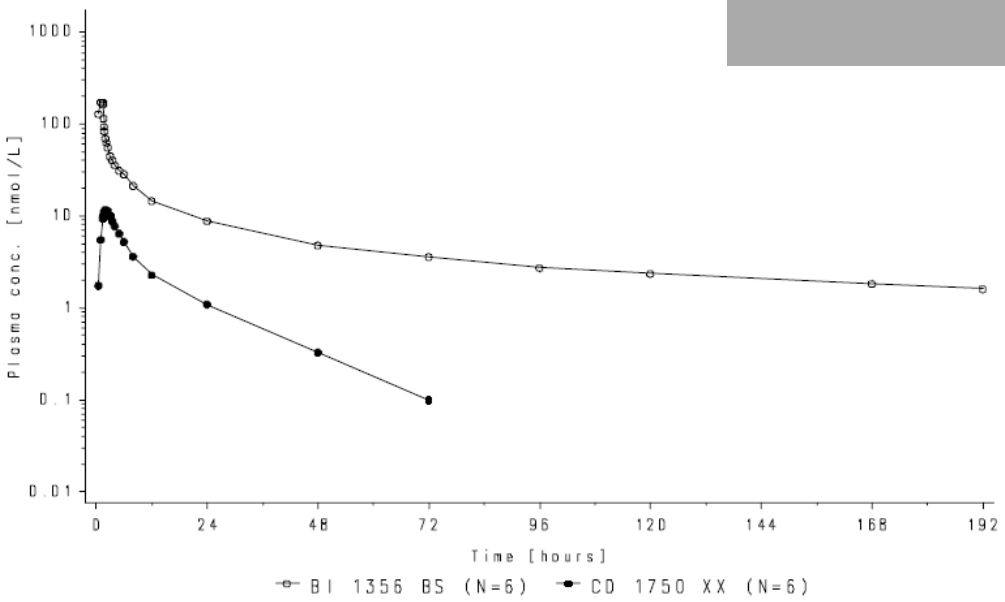


Figure 18: Arithmetic mean plasma concentration-time profiles of linagliptin and CD 1790 after intravenous infusion of 10 mg linagliptin.

Reviewer's comment

In earlier reports, the sponsor denominated main metabolite as CD 1750, which was the racemate used in the calibration curve for quantitation of metabolite. However, later they identified that only the S-enantiomer CD 1790 is generated as the metabolite. Therefore, CD 1750 in earlier reports actually represented the CD 1790.

PK after multiple rising doses (patients with T2DM)

Two Phase 1 studies 1218.2 and 1218.3 evaluated multiple dose pharmacokinetics of linagliptin for doses ranging from 1 mg to 10 mg.

Phase 1 study 1218.2 (12 days duration)

Multiple-dose PK for linagliptin were also non-linear for the studied dose range of 1 mg to 10 mg. The plasma concentration – time profiles from this study are shown in Figure 19 and pharmacokinetic parameters are listed in Table 6. Steady-state C_{max} and AUC also increased in less than dose proportional manner with rising doses from 1 mg to 10 mg. The time required to attain steady-state decreased with increase in dose. For dose groups 1 mg, 2.5 mg, and 5 mg steady-state was reached between days 4 and 7, while for 10 mg dose steady-state was already reached by day 2 (Figure 19). This also suggests that terminal half-life, which ranged from 121 to 131 hours at steady-state, does not predominantly contribute to accumulation. The accumulation half-life determined based on observed accumulation ratio (calculated as $t_{1/2,\ accumulation} = \tau.\ln 2/\ln(R_{A,AUC}/(R_{A,AUC}-1))$ was ~12 hours for 5 mg dose. Accumulation was moderate (RA ~ 1.2 to 2.0) and decreased with increasing doses. The peak-to-through-fluctuation (PTF) was in the range of 40% for the two lower dose groups and about 90% for the two higher dose groups. The renal excretion of the parent compound appeared to be a minor pathway of elimination accounting for about 6% of the total clearance in the 5 mg dose group (data not shown).

The amount excreted in urine increased with dose. Both CL/F and V/F increased with increase in dose. CL/F increased by a factor of 4.3 and V/F by a factor of 4.6 for increase in dose from 1 to 10 mg.

Reviewer's comment
The measured terminal half-life of linagliptin is longer than the accumulation half-life. One possible explanation for this behavior is the dose dependent binding of linagliptin to DPP-4. At lower linagliptin concentrations of 1-3 nM approximately 98% remains bound to DPP-4, at 30 nM it declines to 89%, and at 300 nM it further declines to 84%. The proportion which remains unbound undergoes elimination and turnover of this unbound drug after administration of multiple doses determines the accumulation. Since total (unbound + bound) concentrations of linagliptin are measured, possibly the bound part of the drug contributes to the longer half-life.

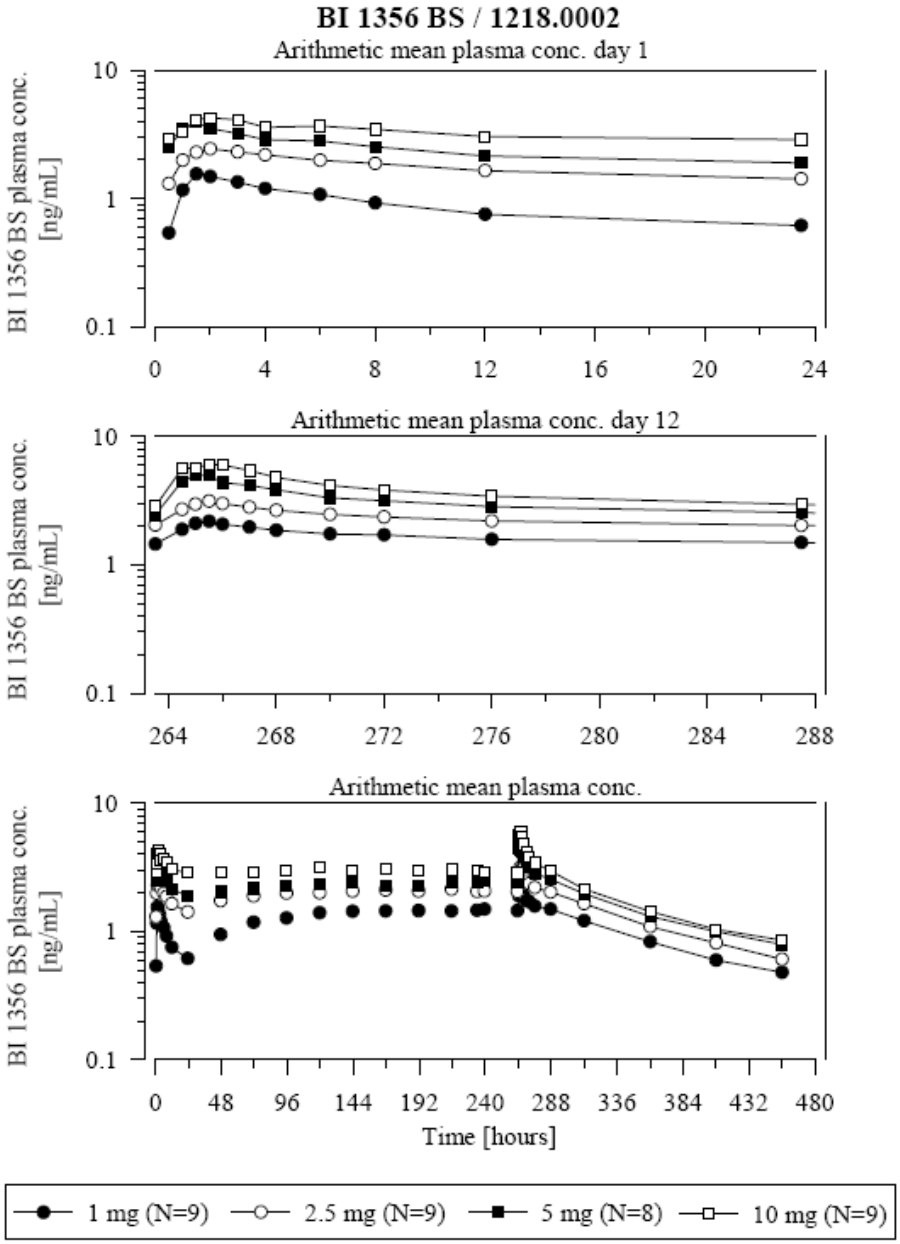


Figure 19: Arithmetic mean drug plasma concentration-time profiles of linagliptin after oral administration of 1 mg, 2.5 mg, 5 mg or 10 mg linagliptin (BI 1356 BS) once daily for 12 days to patients with T2DM (semi-logarithmic scale)

Table 6: Key pharmacokinetic parameters after multiple oral administration of 1 mg to 10 mg linagliptin in a 12-day long study 1218.2

Dose (mg)	N	T_{max} (hour) Median (range)	gMean (gCV%)*								
			Single-dose		Steady-state (day 12)					Accumulation	
			C_{max} (nM)	AUC_{0-24} (nM hr)	$C_{max,ss}$ (nM)	$AUC_{\tau,ss}$ (nM hr)	$t_{1/2,ss}$ (hour)	$CL/F_{,ss}$ (mL/min)	$V_z/F_{,ss}$ (L)	$R_{A,Cmax}$	$R_{A,AUC}$
1	6	1.5	3.1	40.2	4.5	81.7	121	431	4510	1.44	2.03
		(1-3)	(43)	(40)	(29)	(28)	(21)	(28)	(32)	(26)	(31)
2.5	6	2.0	5.3	85.3	6.6	117	113	757	7400	1.25	1.37
		(1-3)	(25)	(23)	(23)	(16)	(10)	(16)	(13)	(11)	(8)
5	6	1.8	8.3	118	11.1	158	131	1120	12700	1.33	1.33
		(0.9-6)	(42)	(16)	(22)	(10)	(17)	(10)	(18)	(30)	(15)
10	6	2	6.7	161	13.6	190	130	1850	20800	1.40	1.18
		(1.5-6)	(30)	(16)	(30)	(17)	(12)	(17)	(23)	(48)	(23)

*gMean= geometric mean and gCV%=geometric CV%

Phase 1 study 1218.3 (4 weeks duration)

This trial evaluated the PK for once-daily oral administration of linagliptin at dose levels of 2.5 mg, 5 mg, and 10 mg, with a relatively higher number of subjects at each dose (see Table 7). The plasma concentration-time profiles from this trial are shown in Figure 20 and the PK parameters are summarized in Table 7. As previously stated, C_{max} and AUC_{0-24} after single-dose and $C_{max,ss}$ and $AUC_{\tau,ss}$ at steady-state increased in less than proportional manner with increase in dose.

Clearance and volume of distribution increased with increase in doses. C_{max} of linagliptin after single dose administration was comparable with the steady state $C_{max,ss}$ within each dose group. The accumulation of linagliptin was below 1.3 based on both peak concentrations and exposure and there was almost no accumulation for the 10 mg dose, probably because of relatively higher clearance. Trough plasma concentrations taken on days 2, 6, 12, 19, 26, 27, and 28 indicate that steady state for linagliptin was reached within 6 days. Based on the accumulation ratio, the effective half-life (or accumulation half-life) would be in the range of 6-10 hours.

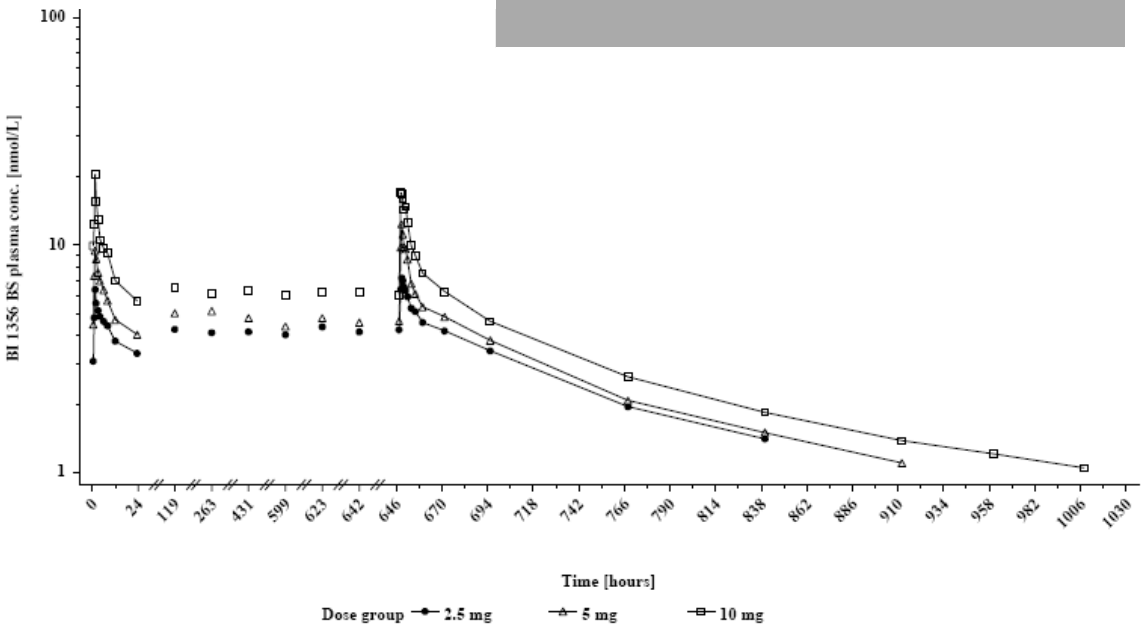


Figure 20: Arithmetic mean drug plasma concentration-time profiles of linagliptin (BI 1356 BS) after oral administration of 2.5, 5 and 10 mg linagliptin once daily for 28 days to patients with type 2 diabetes (semi-log scale)

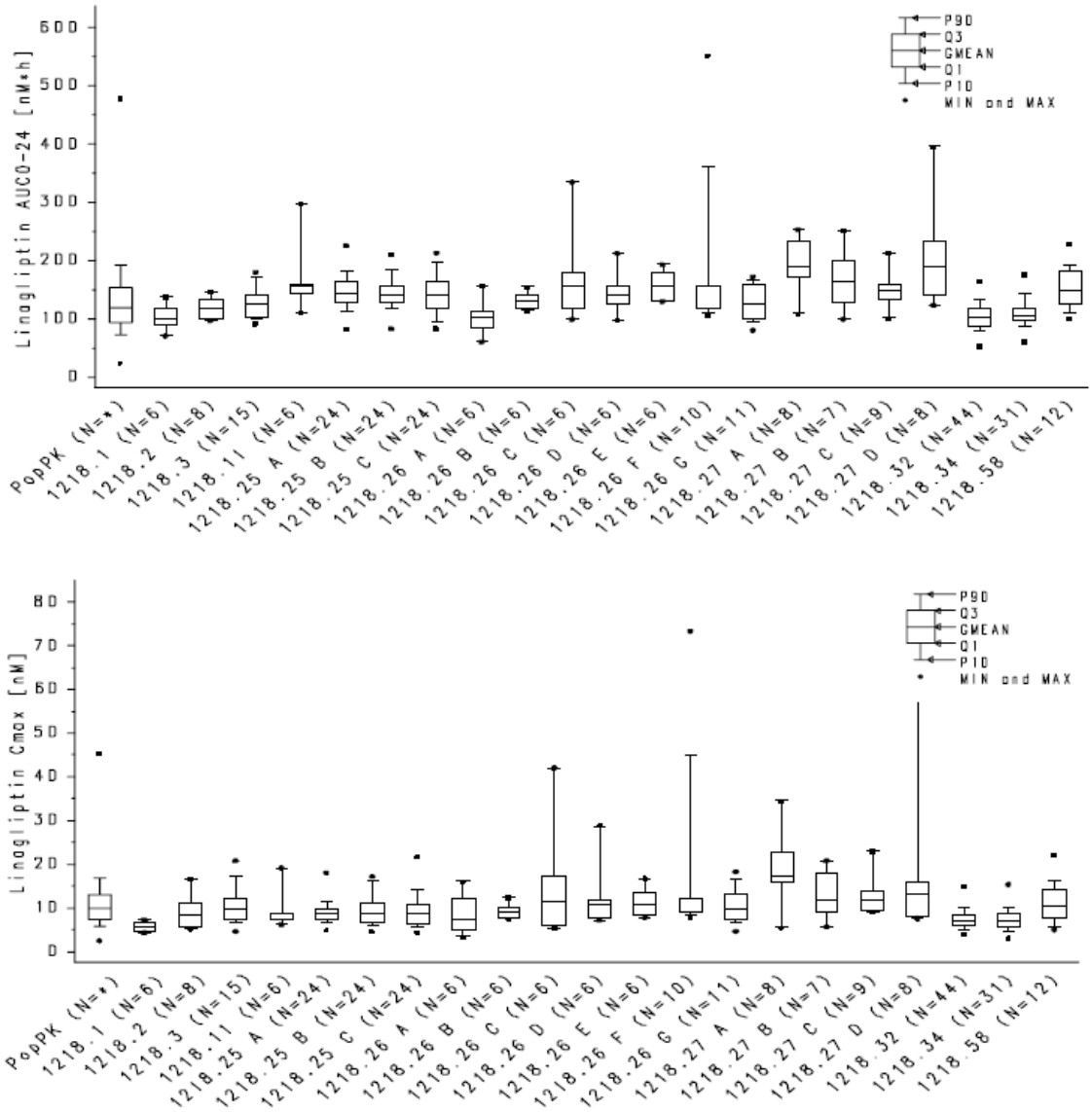
Table 7: Key pharmacokinetic parameters after multiple oral administration of 2.5 mg to 10 mg linagliptin in a four-week long study 1218.3

Dose (mg)	N	T_{max} (hour) Median (range)	gMean (gCV%)*								
			Single-dose		Steady-state (day 28)					Accumulation	
			C_{max} (nM)	AUC_{0-24} (nM hr)	$C_{max,ss}$ (nM)	$AUC_{\tau,ss}$ (nM hr)	$t_{1/2,ss}$ (hour)	$CL/F_{,ss}$ (mL/min)	$V_z/F_{,ss}$ (L)	$R_{A,Cmax}$	$R_{A,AUC}$
2.5	26	1.5 (0.5-8.0)	6.1 (42)	93.1 (28)	7.4 (28)	116 (21)	183 (21)	785 (21)	12000 (28)	1.22 (34)	1.25 (19)
5	15	2.0 (1.0-6.2)	9.6 (39)	124 (20)	12.3 (40)	148 (19)	194 (15)	1190 (19)	20000 (29)	1.29 (41)	1.20 (20)
10	19	1.5 (1.0-8.0)	18.8 (65)	188 (33)	18.6 (56)	207 (27)	203 (16)	1700 (27)	30000 (25)	0.99 (87)	1.10 (30)

*gMean= geometric mean and gCV%=geometric CV%

2.2.7.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

The PK of linagliptin in healthy subjects and patients with T2DM is comparable. Figure 21 and Figure 22 displays the comparison of AUC and C_{max} after single-dose and at steady-state from different trials enrolling healthy subjects or patients with T2DM. The ranges of AUC and Cmax from these two populations are overlapping, except a few cases such as patients with severe renal impairment or moderate hepatic impairment.



Mediaction taken fasted except for population PK analyis, where the medication could be taken with or without food

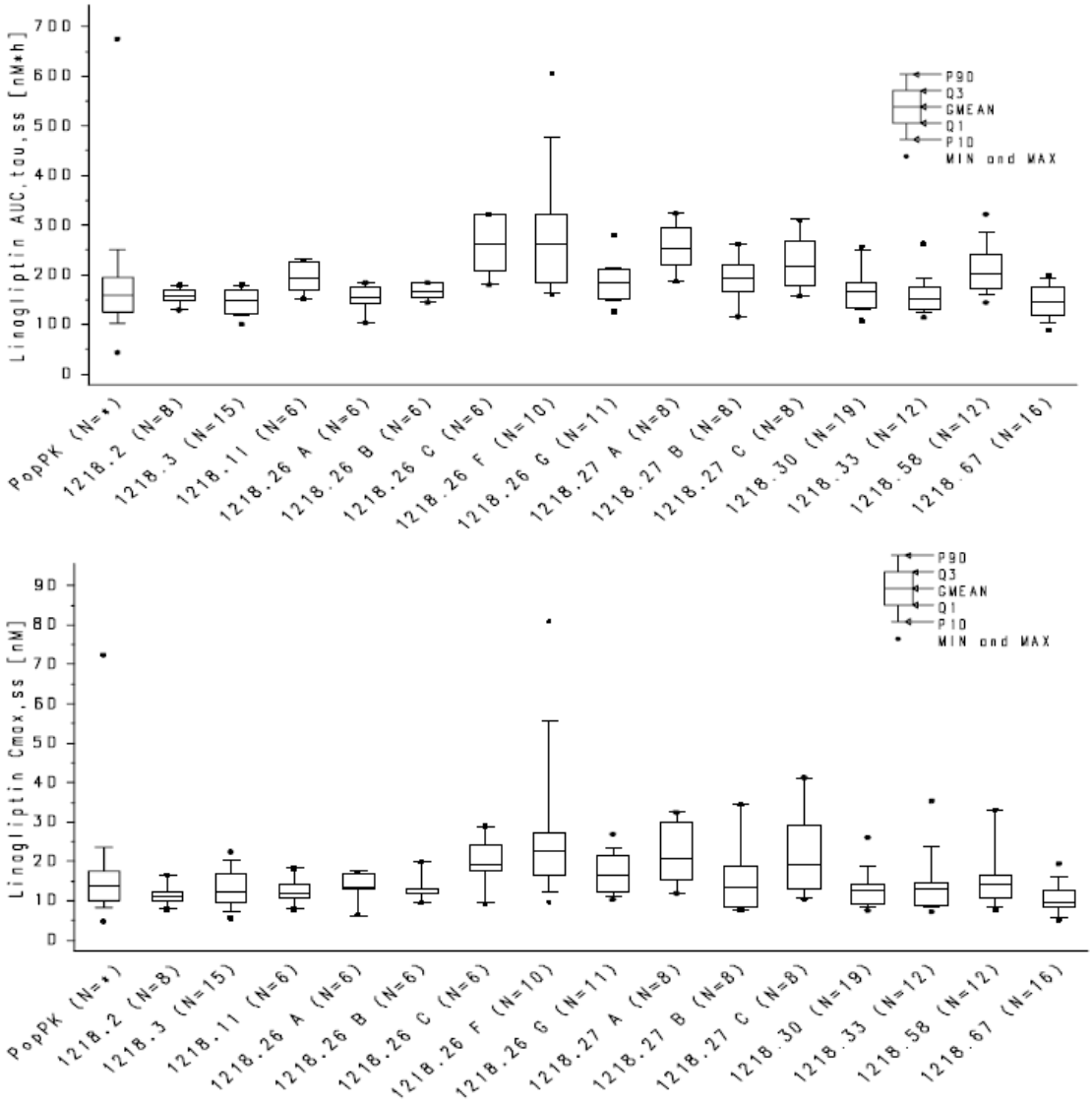
* Values from Population PK analysis were obtained after simulation of 1000 trials. The simulation reflects the linagliptin exposure of male patients receiving 5 mg linagliptin once daily, with no metformin co-treatment and an absorption rate constant of 0.441 1/h (taken from the Phase IIb studies). For the continuous covariates weight, age, gammaglutamyl transferase and baseline DPP-4 activity no influence was assumed (i.e. the median values of the population were used).

1218.26 (renal impairment study) groups: A - healthy controls; B- mildly impaired patients; C- moderately impaired patients; D- severely impaired patients; E – ESRD patients; F – severly impaired T2DM patients; G – T2DM patients with normal renal function

1218.27 (hepatic impairment study) groups: A - healthy controls; B- mildly impaired patients; C- moderately impaired patients; D- severely impaired patients

- **Subjects with T2DM:** 1218.2, 1218.3, 1218.26
- **Healthy subjects:** 1218.1, 1218.25, 1218.30, 1218.32, 1218.34, 1218.67, 1218.26, 1218.27
- **Healthy Japanese subjects:** 1218.11
- **Healthy Chinese subjects:** 1218.58

Figure 21: Box plots showing no difference in single-dose AUC_{0-24} and C_{max} values between healthy volunteers and patients after administration of 5 mg linagliptin



Mediaction taken fasted except for population PK analysis, where the medication could be taken with or without food

* Values from Population PK analysis were obtained after simulation of 1000 trials. The simulation reflects the linagliptin exposure of male patients receiving 5 mg linagliptin once daily, with no metformin co-treatment and an absorption rate constant of 0.441 1/h (taken from the Phase IIb studies). For the continuous covariates weight, age, gammaglutamyl transferase and baseline DPP-4 activity no influence was assumed (i.e. the median values of the population were used).

1218.26 (renal impairment study) groups: A- healthy controls; B- mildly impaired patients; C- moderately impaired patients; D- severely impaired patients; E- ESRD patients; F- severely impaired T2DM patients; G- T2DM patients with normal renal function

1218.27 (hepatic impairment study) groups: A - healthy controls; B- mildly impaired patients; C- moderately impaired patients; D- severely impaired patients

- **Subjects with T2DM:** 1218.2, 1218.3, 1218.26
- **Healthy subjects:** 1218.30, 1218.33, 1218.67, 1218.26, 1218.27
- **Healthy Japanese subjects:** 1218.11
- **Healthy Chinese subjects:** 1218.58

Figure 22: Box plots showing no difference in steady-state $AUC_{\tau,ss}$ and $C_{max,ss}$ values between healthy volunteers and patients after administration of 5 mg linagliptin

2.2.7.3 What are the characteristics of drug absorption?

Linagliptin is rapidly absorbed, with a median time to reach maximum plasma concentration (t_{max}) of ~1.5 h (range: 0.5–8.0 h) after single and multiple dosing, suggesting pre-dominant absorption in the upper intestine. The absolute bioavailability of linagliptin after oral (p.o.) administration of 10 mg dose is approximately 30% (study 1218.10 in section 2.2.8.1). Data from non-clinical studies and drug-drug interaction studies suggest that linagliptin is a P-gp substrate (see section 2.4.1.4). The rate of absorption was reduced when linagliptin was given with food (median t_{max} increased from 1.02 to 2.99 hours and C_{max} was reduced by about 15% (95% CI: 75.9 to 94.6%)), but there was no effect of food on the extent of absorption (see section 2.5.3).

2.2.7.4 What are the characteristics of drug distribution?

In vitro studies indicate tight binding of linagliptin to peripheral tissues, which is assumed to be as a result of binding to peripheral DPP-4. The volume of distribution at steady-state (Vss) following a single 90 minute intravenous infusion of 5 mg linagliptin to healthy subjects was approximately 1110 liters, which exceeds the total body volume and indicates that linagliptin distributes extensively into human tissues.

Plasma protein binding of linagliptin in human plasma is concentration-dependent (Figure 23). The plasma protein binding at human therapeutic concentrations is mainly determined by DPP-4. Binding of linagliptin to isolated human serum albumin (f_B = 48.2%) and human alpha-1 acid glycoprotein (f_B = 32.8%) dissolved in buffer was lower than the bound fraction observed at high plasma concentrations of linagliptin (f_B ~78% at comparable concentrations).

The binding of linagliptin to DPP-4 reduced from 98.8% for 2 nM to about 83% for 20 nM (Figure 23). The more than 10 fold increase in unbound fraction between 2 to 20 nM reflects saturation of binding to DPP-4 with increasing concentrations of linagliptin. At supratherapeutic concentrations above 100 nM, the plasma protein binding becomes stable with a bound fraction between about 70 to 80% (Figure 23).

In mass balance study (see study 1218.7 in individual study reports), distribution of [^{14}C] linagliptin into red blood cells was found to be negligible after oral administration of 10 mg dose (Mean maximum $C_{bloodcells}/C_{plasma}$ ratio of 0.0668). In *ex vivo* studies, distribution of [^{14}C] radioactivity into blood cells was found to be concentration-dependent, increasing with rising linagliptin concentrations. This concentration dependency is possibly due to the binding of linagliptin to plasma DPP-4, with substantial distribution into erythrocytes only after saturation of plasma DPP-4.

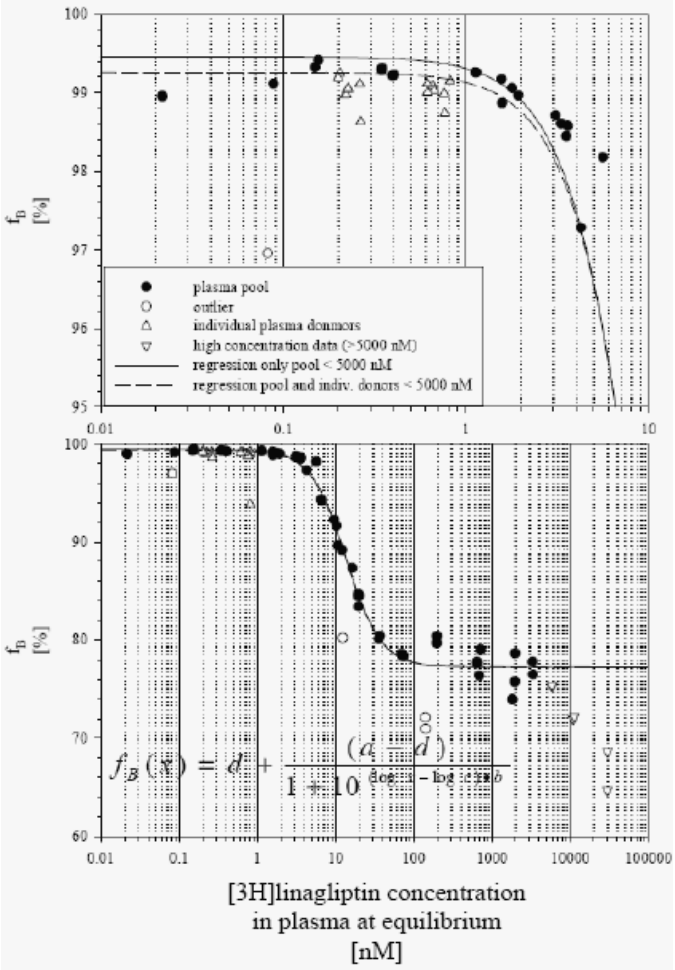


Figure 23: Concentration dependency of the plasma protein binding of [^{3}H] linagliptin in human plasma including the plot of non-linear regression (formula given in the plot)

2.2.7.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

At 10 mg oral dose renal elimination contributes to <5% in linagliptin elimination (Table 8). However, after intravenous infusion, about 31% of total radioactivity was excreted in the urine (Table 9); the difference was possibly due to the higher unbound concentrations of linagliptin after intravenous administration and also possibly because of the incomplete bioavailabilty after oral administration. Therefore, based on mass balance study for the proposed oral route of administration renal elimination is not the major elimination pathway for doses up to 10 mg.

After intravenous infusion administration of [^{14}C] linagliptin ~44% of total radioactivity was recovered in feces as unchanged drug (Table 9). Appearance of unchanged drug in feces after intravenous administration is likely mediated by entero-hepatic recycling of parent drug and/or its metabolites. This is further supported by existence of double peaks in plasma concentration-time profiles within the first 6 hours after oral administration. Because of enterohepatic recycling property of linagliptin hepatic route of elimination appears to be an important elimination pathway. However, note that ~85% elimination of

linagliptin in feces after oral administration (Table 8) will also have some fraction of drug which was not absorbed (i.e., incomplete bioavailability).

Table 8: Metabolite pattern in urine and feces after a single oral dose of 10 mg (21.2 µmol) [^{14}C] linagliptin (BI 1356 BS) (arithmetic mean of 6 individuals)

metabolite	urine 0 - 48 h	faeces 0 - 120 h	urine + faeces total
BI 1356	**3.9**	**74.1**	**78.0**
M474(1)	0.2	0.3	0.5
M489(1)	0.2	4.5	4.7
M503(1)	< 0.1	0.1	0.1
M504(2)	0.1		0.1
M515(1)	0.1		0.1
M531(2) + M490(1) + M506(1)		2.5	2.5
M650(1)	0.3		0.3
M665(3)	0.1		0.1
M665(8) + M490(1)	0.3		0.3
m1	0.1		0.1
m2	0.2		0.2
m3	< 0.1		< 0.1
m5	< 0.1		< 0.1
m6	< 0.1		< 0.1
total	5.5	81.5	87.0

empty cells: not detected

Table 9: Metabolite pattern in urine and faeces after a single intravenous infusion dose of 5 mg (10.6 µmol) [^{14}C] linagliptin (BI 1356 BS) (arithmetic means of 6 individuals)

metabolite	urine 0 - 48 h	faeces 0 - 240 h	urine + faeces total
BI 1356	**25.3**	**35.8**	**61.1**
M474(1)	0.1	2.5	2.6
M476(1) + M515(1)	0.1		0.1
M489(1)	0.3	9.3	9.6
M503(1)	0.2	1.2	1.4
M506(1)		4.0	4.0
M620(1)	< 0.1		< 0.1
M636(2)	0.1		0.1
M636(3,4)	0.2		0.2
M665(3)	0.4		0.4
M665(8) + M531(1,2)	0.7		0.7
m1	< 0.1		< 0.1
m2	0.1		0.1
m3	< 0.1	0.3	0.4
m5	< 0.1		< 0.1
total	27.5	53.2	80.7

empty cells: not detected

2.2.7.6 What are the characteristics of drug metabolism?

Metabolism is a minor elimination pathway and unchanged parent compound was the most abundant component in urine, feces, bile, and plasma. Approximately 90% of the drug after oral administration of a single 10 mg dose is eliminated as unchanged drug (Table 8). Several minor metabolites were formed by oxidation followed by glucuronic acid conjugation, but no single metabolic reaction was particularly predominant. The metabolite profile of linagliptin in humans is shown in Figure 24. A Phase-I metabolite, CD 1790 (or M474(1) in Figure 24 and Table 8 and Table 9) was formed in humans, rats, and Cynomolgus monkeys which exceeded 10% of plasma radioactivity. CD 1790 is about 1000 times less active than linagliptin. *In vitro* metabolism of [^{14}C] linagliptin by human liver microsomes and human hepatocytes was also very low, supporting the finding that linagliptin is predominantly excreted unchanged in humans.

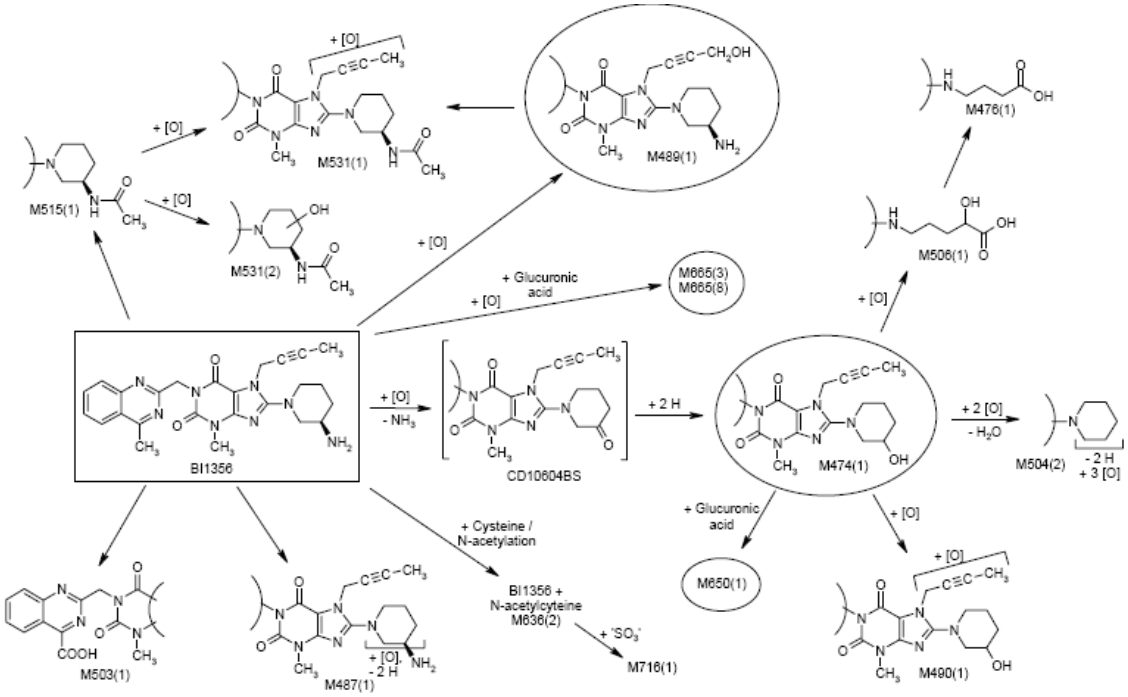


Figure 24: Human metabolism pathways of [^{14}C] linagliptin (BI 1356 BS) (rectangle) after intravenous and oral administration; Metabolites in excreta and plasma (circle)

M474(1) or CD1790, with the amino group of the piperidine moiety substituted by a hydroxy group was identified as the major metabolite. Additional minor metabolites formed by combined phase I oxidation and glucuronide conjugation were: M489(1) formed by oxidation of the methyl group of the butinyl side chain, M665(3) and M665(8) were formed by glucuronidation of mono oxidized derivatives of linagliptin. Subsequent oxidation and condensation steps at the piperidine moiety formed metabolite M487(1). The oxidation of the methyl group in 4 position of the quinazoline moiety let to the corresponding carboxylic acid derivative M503(1). Subsequent oxidation of M474(1) at the butinyl side chain formed metabolite M490(1) and at the piperidine moiety formed metabolites M504(2), M506(1) and M476(1). M650(1) was formed by conjugation of M474(1) with glucuronic acid. The *N*-acetyl derivatization of parent compound formed

metabolite M515(1), and subsequent oxidation of butinyl side chain and the piperidine moiety formed metabolites M531(1) and M531(2), respectively. A cysteine adduct of the parent compound formed metabolite M636(2) and its sulfate conjugate was additionally observed.

2.2.7.7 What are the characteristics of drug elimination?

After oral administration of linagliptin 10 mg dose to healthy subjects, about 80% of the drug was eliminated unchanged in feces and about 5% was eliminated in urine within 96 hours of dosing.

2.2.7.8 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Linagliptin exposure increased in less than proportional manner with dose after single oral doses of 0.5 to 10 mg (Trials 1218.1,1218.2, and 1218.3), single intravenous doses of 0.5 to 10 mg (Trial 1218.10), and after multiple administration of once-daily dose of 1 mg to 10 mg in healthy subjects and patients (Trials 1218.2, 1218.3, and 1218.33). Please refer to individual study reports for data from each individual study.

The geometric mean values for single-dose PK (i.e., dose normalized C_{max} and AUC) from trials 1218.1, 1218.2, 1218.3, and population PK analysis are summarized in Figure 25. We observe a decrease in these dose normalized metrics with increase in dose from 0.5 mg to 10 mg, indicating less than dose proportional increase in exposure with increase in dose. Similar less than proportional behavior was also observed for steady-state $C_{max,ss}$ or $AUC_{\tau,ss}$ in dose range of 1 to 10 mg (Figure 26).

This less than dose proportional behavior can be explained by concentration dependent binding of linagliptin to DPP-4 (see section 2.2.7.4). Linagliptin $C_{max,ss}$ increases from 4.5 nM to 19 nM with increase in dose from 1 mg to 10 mg (Table 6 and Table 7), correspondingly the unbound fraction increases from approximately 1% to about 16% based on Figure 23. As a result, the relative elimination of linagliptin increases because unbound fraction is also the fraction that undergoes elimination. As a consequence, the pharmacokinetic parameters, which remain constant independent of administered dose for drugs with linear pharmacokinetics (e.g. clearance, volume of distribution, and fraction excreted renally) increase in the case of linagliptin following increase in linagliptin dose.

For doses beyond 10 mg, a more than proportional increase in exposure was observed with increase in dose from 25 mg to 100 mg, and almost statistically proportional behavior was observed for doses between 100 mg and 600 mg (Figure 27). The more than proportional behavior and the subsequent proportional behavior could possibly be explained by interaction of linagliptin with ABCB1 (P-glycoprotein) transporter. The IC_{50} value for P-gp inhibition is 55 μM suggesting that inhibition at lower doses (with low nM concentrations) would be minimal and would become more prominent at higher doses. At dose of 25 mg the C_{max} of linagliptin is 72 nM (Table 4) and the corresponding plasma protein binding (as shown in Figure 23) is about 82%, which remains almost stable at 80% for further higher concentrations (Figure 23). Therefore at these higher

doses higher unbound concentrations of linagliptin would be available for interaction with ABCB1.

Opposite to linagliptin, metabolite CD1790 PK demonstrated more than proportional increase in exposure with increasing dose from 1 mg to 5 mg (Figure 28), indicating that with increase in unbound drug concentration the proportion of drug undergoing metabolism increases.

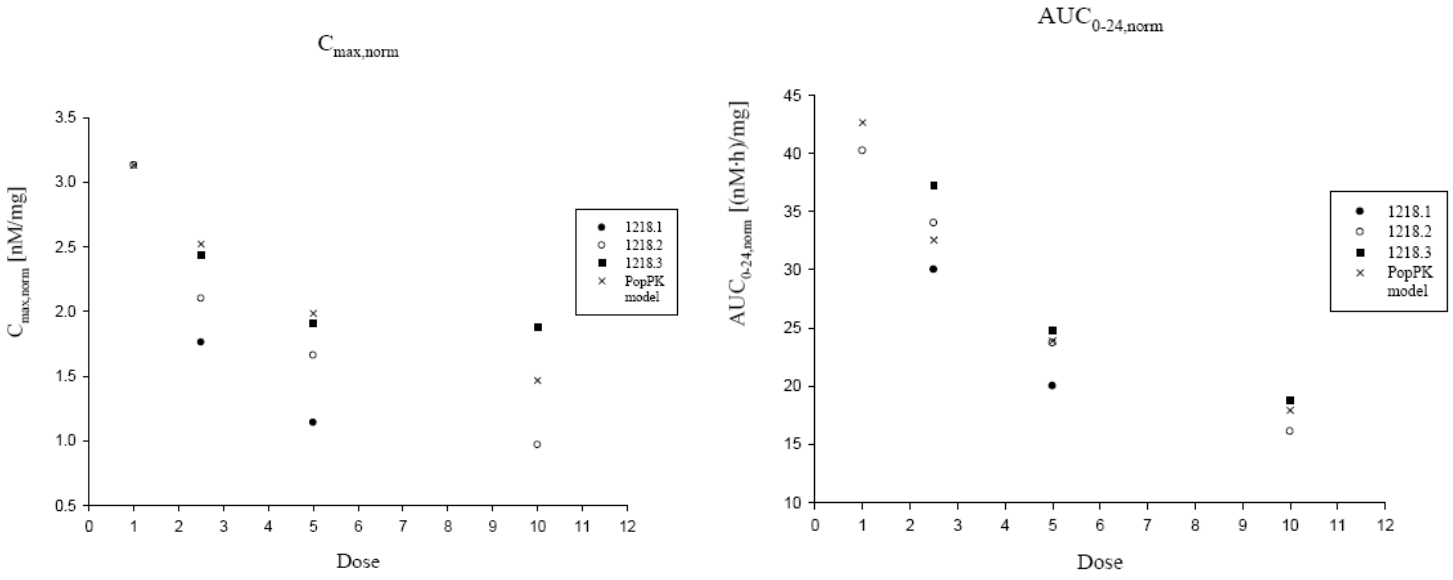


Figure 25: Dose normalized single-dose AUC and Cmax geometric mean values in therapeutic dose range of 1 mg to 10 mg measured in Caucasian healthy volunteers and patients

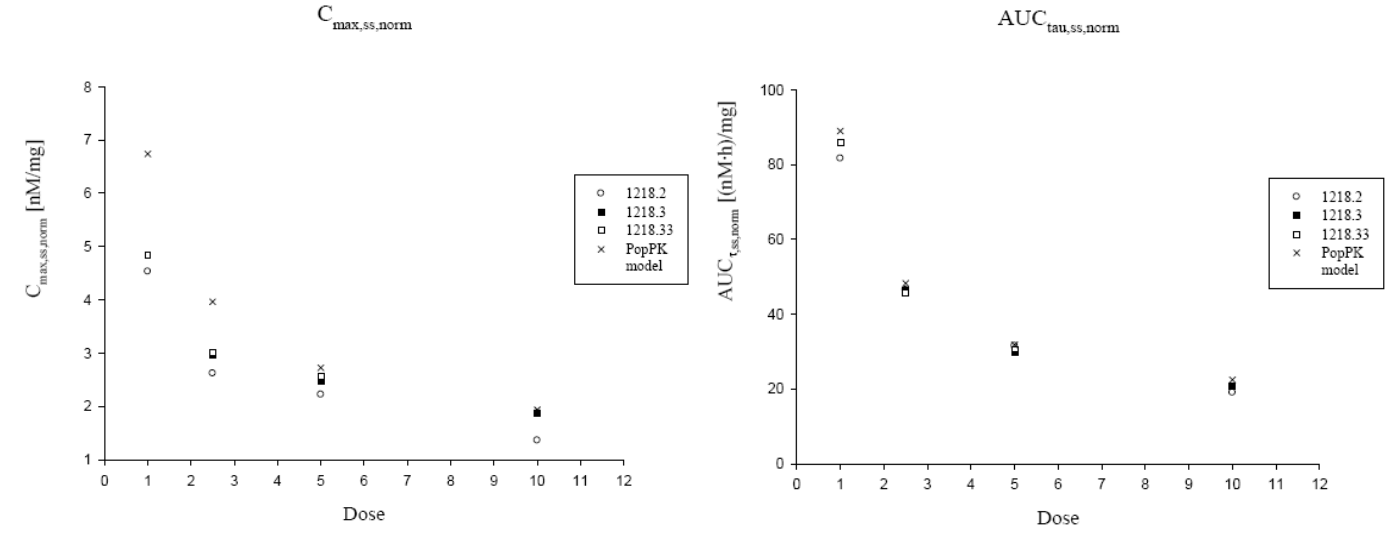


Figure 26: Dose normalized steady-state (multiple-dose) AUC and C_{max} geometric mean values in therapeutic dose range of 1 mg to 10 mg measured in Caucasian healthy volunteers and patients

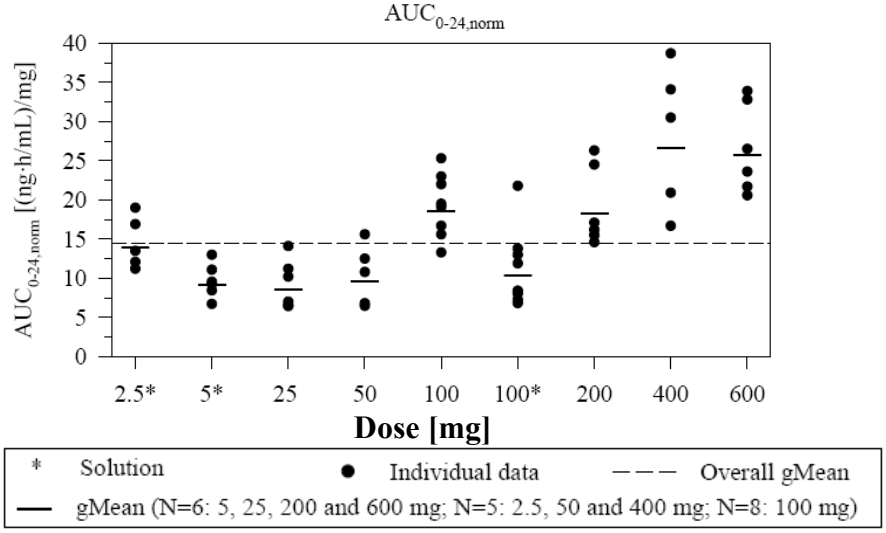


Figure 27: Dose normalized AUC values of linagliptin (BI 1356 BS) after single oral administration of doses ranging from 0.5 mg to 600 mg in single rising dose trial 1218.1

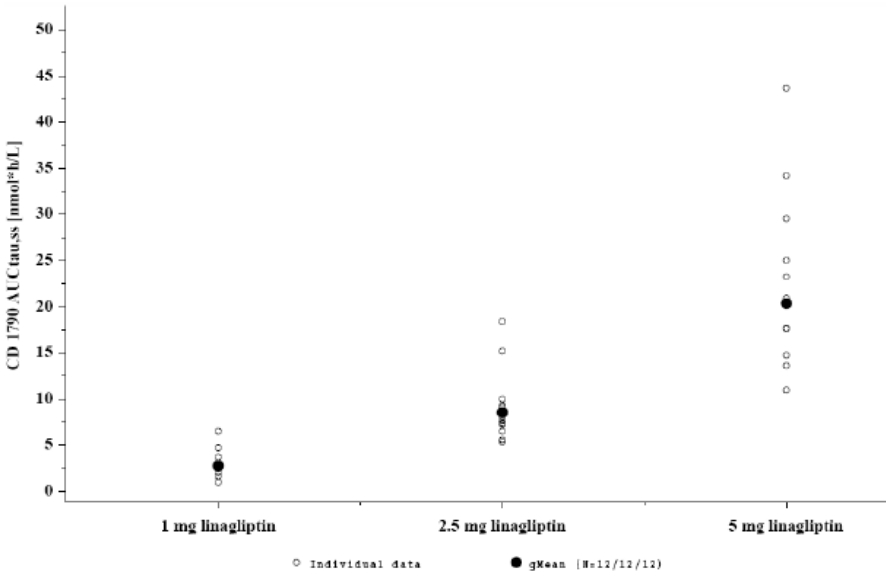


Figure 28: Dose normalized AUC values of <u>CD 1790 at steady-state</u> after oral administration of doses ranging from 1 mg to 5 mg in dose proportionality trial 1218.33

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Renal impairment alters the linagliptin exposure as described below. Available data suggest no clinically relevant impact of race, age, gender, and hepatic impairment on linagliptin PK.

2.3.1.1 Age, BMI, Weight, and Gender

The influence of covariates age, BMI, gender and weight on linagliptin PK were evaluated in the population PK analysis. The analysis included 302 male and 160 female patients aged between 30 and 78 years, with a weight ranging from 57 to 132 kg and a BMI ranging from 20.4 to 42.2 kg/m^2. Note that BMI was not included as a covariate for population PK analysis *a priori* and its impact was only assessed using observed data (see points (B) and (C) below). Age and gender were statistically significant covariates for BMAX (model parameter representing the typical concentration of binding site in central compartment) and weight was a statistically significant covariate for F1 (absolute bioavailability) and V2 (central volume of distribution). However, sponsor reported that effect of these covariates on linagliptin exposure was not clinically relevant, as described below:

(A) Effect of covariates on predicted $AUC_{\tau,ss}$ based on simulations by Berkley Madonna using the population PK model

Based on the final population PK model, typical plasma concentration –time profiles were simulated for 5th percentile (P.05), median and 95th percentile (P.95) covariate values for continuous covariates or the respective values for categorical covariates using Berkeley Madonna modeling software. Sponsor performed simulations to assess the impact of single covariate (Table 10); however, we also assessed the impact of combined covariates (Table 11). The $AUC_{\tau,ss}$ was calculated by integrating the PK profiles directly within Berkeley Madonna. Change in these covariates from P.05 to P.95 only had a minor effect (i.e., ± 9%) on linagliptin exposure (see Table 10 and Table 11).

The combination of all covariates in two extreme worst case scenarios – **(a)** an old (73 years), low-weight (67 kg), female patient on metformin medication with high GGT (158 U/L) and high pre-dose DPP-4 activity (18623 RFU), and **(b)** a young (42 years), high-weight (117 kg), male patient with low GGT (9.4 U/L), low pre-dose DPP-4 activity (8025 RFU), and on linagliptin monotherapy– resulted in 26% decrease and 38% increase in $AUC_{\tau,ss}$, respectively. The exposures in range of -26% and +38% were still considered safe and efficacious based on safety profiles from Phase 2 and Phase 3 trials evaluating doses up to 10 mg and efficacy results from trials 1218.5, 1218.6, and 1218.23 (see Figures 8 and 10 under section 2.2.2).

Table 10: Investigation of the impact of single covariate† on $AUC_{\tau,ss}$ after administration of 5 mg linagliptin

Model parameter	Statistically significant covariate	Categories	Typical $AUC_{\tau,ss}$ [nM*h]	%difference from median
F1	WT	P.05 (67 kg)	163.38	+5.9%
		Median (88 kg)	154.23	
		P.95 (117 kg)	140.9	-8.7%
BMAX	AGE	P.05 (42 years)	142.8	-7.4%
		Median (60 years)	154.23	
		P.95 (73 years)	162.5	+5.4%
	SEX	Male	154.23	
		Female	164.65	+6.8%

†For assessment of single covariates effect only one significant covariate was incorporated in the model at a time and covariate values were changed to P.05, median, and P.95 level.

Table 11: Investigation of impact of combined covariates* on $AUC_{\tau,ss}$ after administration of 5 mg linagliptin

Model parameter	Statistically significant covariate	Categories	Typical $AUC_{\tau,ss}$ [nM*h]	%difference from median
F1	WT	P.05 (67 kg)	164	+6.5%
		Median (88 kg)	154	
		P.95 (117 kg)	141	-8.4%
BMAX	AGE	P.05 (42 years)	143	-7.1%
		Median (60 years)	154	
		P.95 (73 years)	163	+5.8%
	SEX	Male	154	
		Female	165	+7.1%

*For assessment of combined covariates effect all the significant covariates were incorporated in the model at their median values assuming male patient, which would provide the $AUC_{\tau,ss}$ for median values (i.e., =154 nM*h). To get the $AUC_{\tau,ss}$ for P.05 and P.95 of a covariate, values for only that covariate were changed to P.05 and P.95 level and other covariates were kept at median values.

(B) Comparison of observed linagliptin trough concentrations between covariate groups for dose levels 0.5 mg, 1 mg, 2.5 mg, 5 mg, and 10 mg

Based on baseline demographic characteristics for Phase 2 trials -1218.5 and 1218.6, observed plasma concentration – time profiles for linagliptin at steady-state were compared between patient groups listed in Table 12. Sponsor reported that patients with a BMI >35 kg/m^2 might have a slightly lower exposure compared to patients with a BMI ≤ 35kg/m^2 (Figure 29). Sponsor also stated that age group >65 years tended to have slightly higher linagliptin levels compared to patients ≤ 65 year old (Figure 30) but no difference was obvious based on gender (Figure 31). These small changes were not considered clinically relevant.

Table 12: Number of patients per study and dose group for investigated categories

	1218.5			1218.6		
	0.5	**2.5**	**5**	**1**	**5**	**10**
BMI > 35	9	14	13	20	20	17
BMI < 25	1	5	3	2	3	5
AGE > 65	12	18	9	17	17	26
AGE > 72	3	6	1	0	6	8
Blacks	3	3	1	0	0	1
Hispanics	4	6	6	0	0	2
Asians	3	1	2	1	0	0
Females	13	30	24	29	29	30

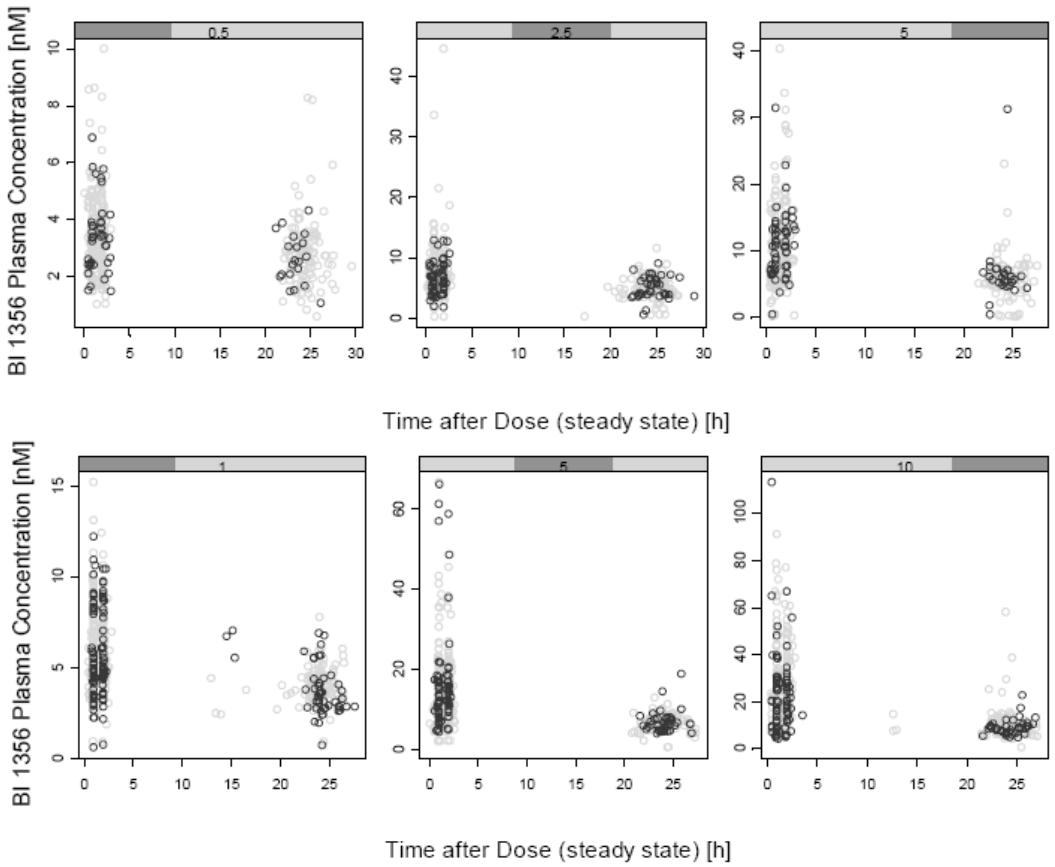


Figure 29: Linagliptin (BI1356) plasma concentration versus time profile at steady state. Dark color circles - patients with a BMI greater than 35 kg/m^2, light color circles - patients with a BMI equal or less than 35 kg/m^2. Top: PK profiles of the 1218.5 study by dose group, Bottom: PK profiles of the 1218.6 study by dose group

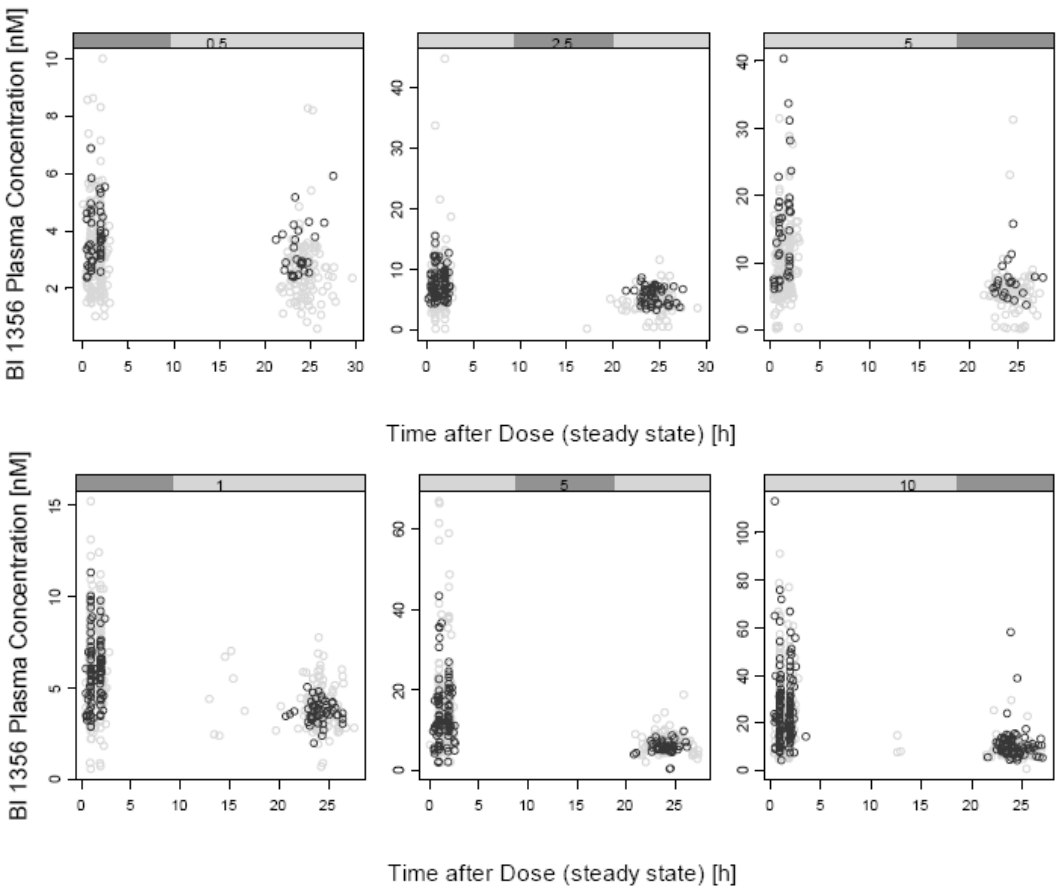


Figure 30: Linagliptin (BI1356) plasma concentration versus time profile at steady state. Dark color circles –patients older than 65 years, light color circles –patients equal and younger than 65 years. Top: PK profiles of the 1218.5 study by dose group, Bottom: PK profiles of the 1218.6 study by dose group

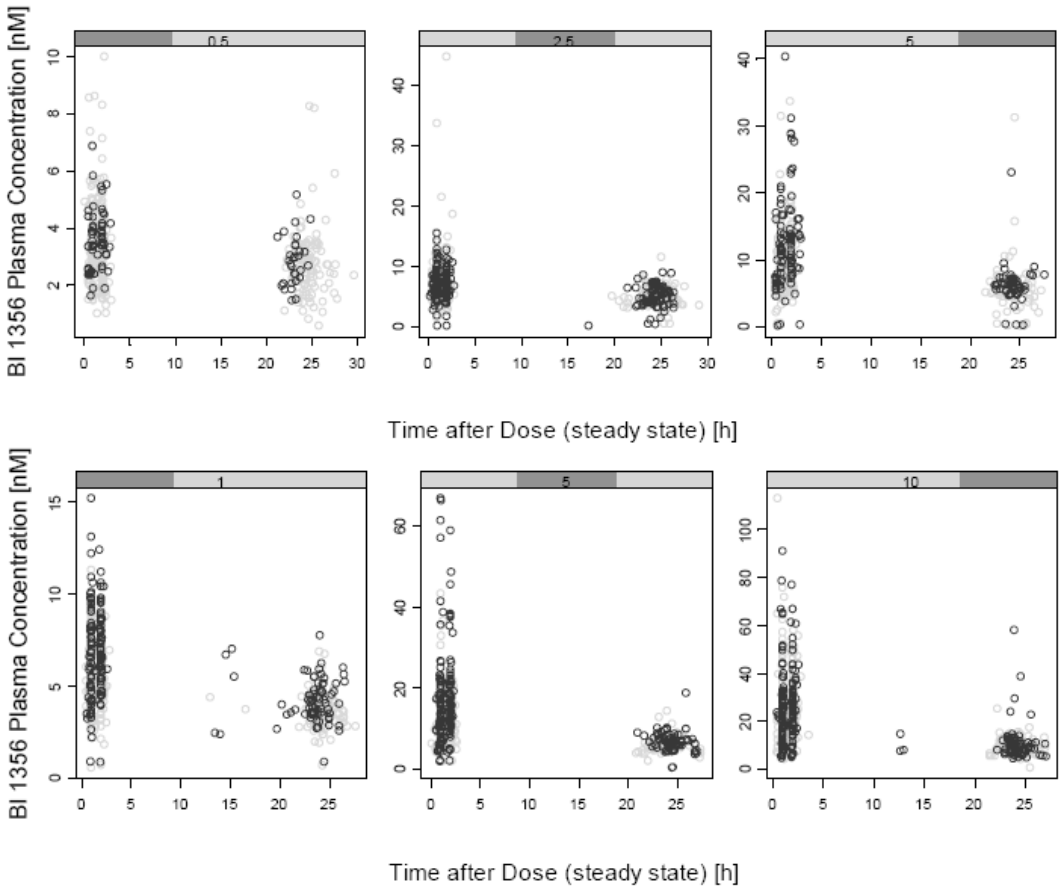


Figure 31: Linagliptin (BI1356) plasma concentration versus time profile at steady state. Dark color circles –females, light color circles –male subjects. Top: PK profiles of the 1218.5 study by dose group, Bottom: PK profiles of the 1218.6 study by dose group

(C) Comparison of observed steady-state trough concentrations and C_{max} for the 5 mg dose between covariate groups

Steady-state C_{max} and trough concentrations for 5 mg dose group from trials 1218.2, 1218.3, 1218.5, and 1218.6 were compared between covariate groups (Figure 32 and Figure 33). Sponsor reported small correlations of covariates age or gender with both trough concentrations and C_{max}. However, none of the tested covariates were reported to have a large impact on the trough concentrations or C_{max}.

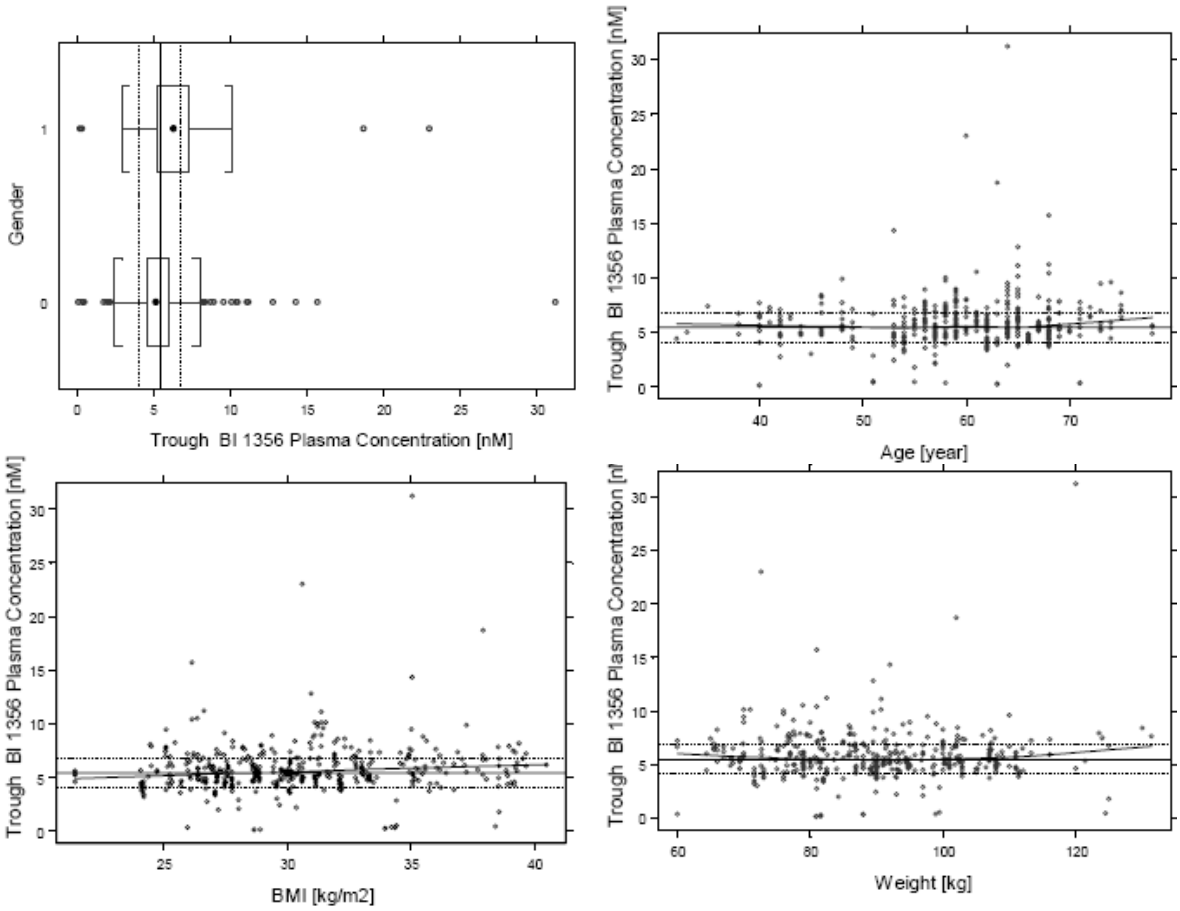


Figure 32: Steady-state linagliptin trough concentrations vs. covariates <u>for 5 mg oral dose group</u>. Horizontal box plot for gender shows the smallest observation, lower quartile, median, upper quartile, and largest observation. In scatter plots the solid straight line shows the median, the dotted straight lines are the median + and – 25 %. Gender: 0-male and 1-female.

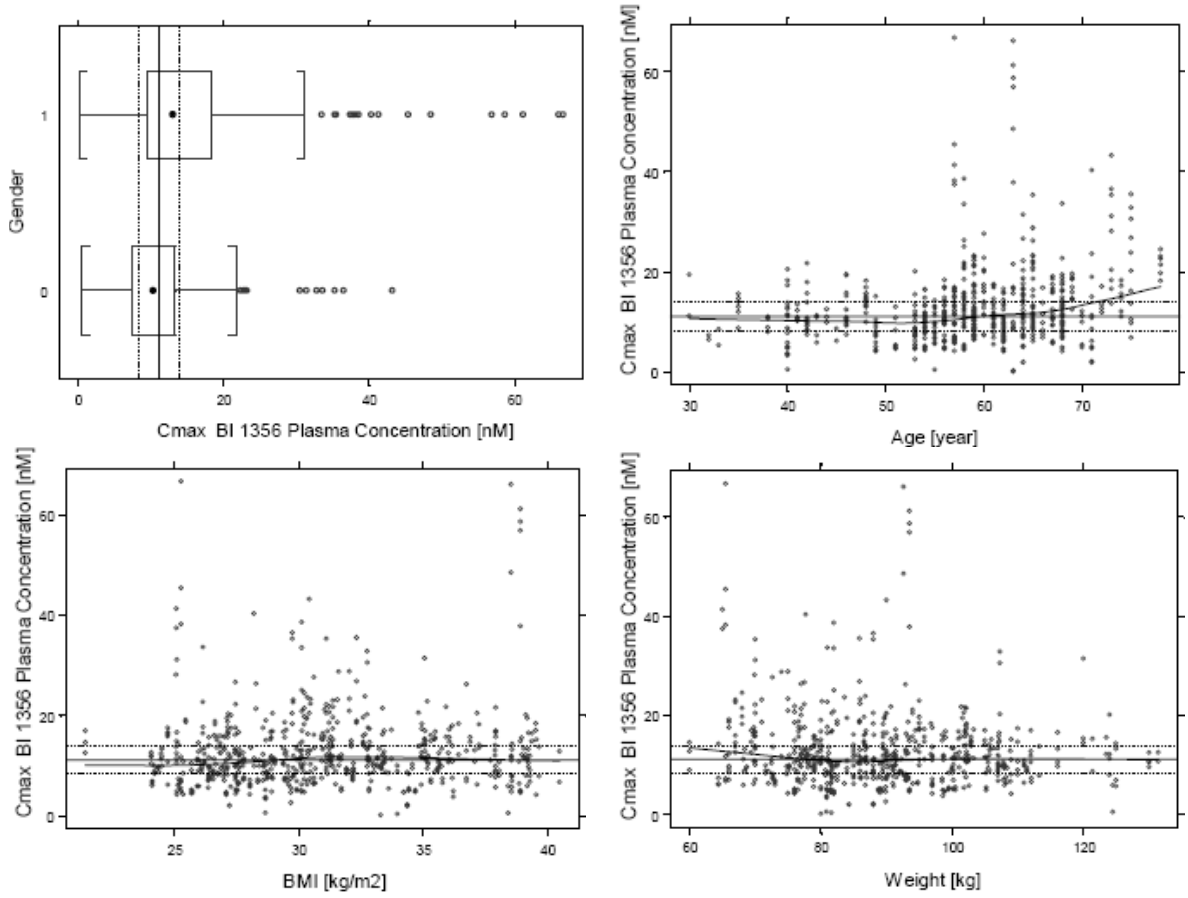


Figure 33: Linagliptin C_{max} at steady-state vs. covariates <u>for 5 mg oral dose group</u>. Horizontal box plot for gender shows the smallest observation, lower quartile, median, upper quartile, and largest observation. In scatter plots the solid straight line shows the median, the dotted straight lines are the median + and – 25 %. Gender: 0-male and 1-female.

Reviewer's comment

Sponsor's conclusion that covariates age, BMI, gender, and weight do not have clinically relevant effect on linagliptin PK is acceptable.

2.3.1.2 Pediatric Patients

Safety and effectiveness of linagliptin in pediatric patients has not been evaluated yet. Sponsor has submitted the pediatric plan which will be presented to PeRC on March 16, 2011. Sponsor has requested a partial waiver for the pediatric population ≤ 9 years of age. For age groups 10 to 17 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 17 years of age, with T2DM and insufficient glycemic control despite treatment with diet and exercise alone, and (2) A randomized, double-blind, 12 week efficacy and safety study of linagliptin, with an extension to 52 weeks, in children from 10 years to 18 years of age with T2DM.

2.3.1.3 Race

In population PK analysis the effect of race was only assessed graphically because of the limited number of non-Caucasian subjects. Sponsor also compared the PK of linagliptin between Caucasian, African-American, Asian, and Hispanic patients based on observed concentrations as stated in points (B) and (C) for section 2.3.1.1. Assessment of PK and PD in African-Americans, Chinese and Japanese patients were supported by clinical trials: 1218.55 (interim analysis), 1218.58, and (1218.11 and 1218.12), respectively.

Population PK analysis

In population PK analysis, race was not found to be a covariate for any PK parameter including clearance (Figure 34).

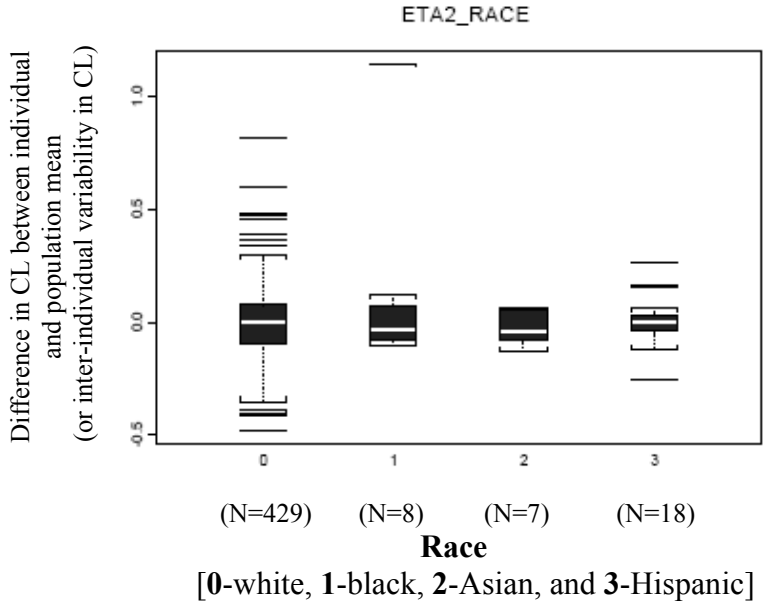


Figure 34: Impact of race on clearance in population PK analysis

Assessment of impact of race based on observed data

Based on comparison of observed steady-state concentrations for the ethnic groups listed in Table 12, sponsor stated that the linagliptin concentrations in black, Asian or Hispanic patients were in the same range as Caucasians; however, only few non-Caucasian patients participated in the studies.

Sponsor also compared the observed trough concentrations and steady-state C_{max} for 5 mg oral dose between ethnic groups based on data from studies 1218.2, 1218.3, 1218.5, and 1218.6. Based on these results sponsor reported no large impact of covariate 'race' on steady-state trough concentrations or C_{max} values (see Figure 35).

Reviewer's comment

Sponsor's conclusion about no impact of race on linagliptin PK based on data shown in Table 12 is not well supported. There are too few patients with Black, Hispanic, and Asian ethnicity to make any meaningful comparisons. However, evaluation of PK in Black or African-American subjects is supported by a separate clinical trial (1218.55, see

below), which showed no clinically relevant differences in PK between African-American and Caucasian subjects. Similarly PK in Asian subjects (i.e., Japanese and Chinese ethnicity) was also evaluated in dedicated clinical trials (1218.58, 1218.11, and 1218.12) and determined no clinically relevant differences compared to Caucasians. Additionally, based on linagliptin disposition profile, metabolism plays minor role in elimination of linagliptin and transporters do not appear to influence PK at therapeutic concentrations reducing the possibility of race based differences in disposition. Therefore, even with limited data it is reasonable to state that there are no clinically meaningful differences in linagliptin PK based on race.

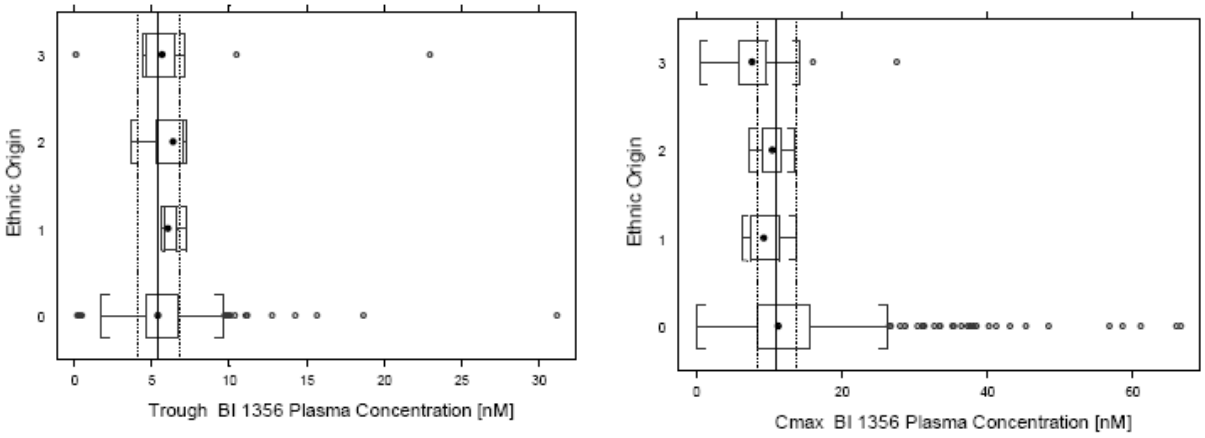


Figure 35: Box-and whisker plot showing linagliptin trough concentrations and C_{max} at steady-state vs. ethnicity for 5 mg oral dose group. Ethnic origin: 0-white, 1-black, 2-Asian, and 3-Hispanic

Trial 1218.55 – evaluation of PK and PD of linagliptin in African-American patients

Sponsor also submitted data from an interim analysis for a trial evaluating the PK and PD of linagliptin 5 mg dose in African-American patients with T2DM. Both single-dose and multiple-dose (7 days) PK and PD were characterized. Results are based on 20 evaluable patients.

Single-dose PK did not appear to be different between African-American and Caucasian patients with T2DM, based on comparison of PK parameters for trials 1218.55 and 1218.3 (Table 13).

Steady-state $C_{max,ss}$ and $AUC_{\tau,ss}$ for African-American patients were ~25% higher than that for Caucasians. However, these exposures were lower than the exposure of 10 mg dose in Caucasians (shown in Table 6 and Table 7), which has been evaluated in Phase 2 studies of up to 12 week duration and in a Phase 3 trial in Japanese patients (Trial # 1218.20). There were no significant safety findings from these trials. Therefore, the ~25% change in exposure were not considered clinically meaningful.

With respect to pharmacodynamic action, the reduction of plasma DPP-4 activity was at least 80% at 24 hours after the last dose in both Caucasian and African-American patients. The 50% and 80% inhibition of DPP-4 in African-American patients was achieved at about concentrations of 3 nM and >5nM, respectively. This concentration range was

similar to that observed for combined analysis of predominantly Caucasian data from trials 1218.2, 1218.3, 1218.5, and 1218.6 (50% and 80% inhibition of DPP-4 at concentrations of about 2.97 nM and 5.30 nM, respectively).

Table 13: Comparison of single-dose and steady-state PK between Caucasian and African-American type 2 diabetic patients from trials 1218.3 and 1218.55, respectively

Trial	1218.3 (in Caucasians)	1218.55† (in African-Americans)
Linagliptin Dose	5 mg (N=15)	5 mg (N=20‡)
Parameter	gMean (gCV%)	gMean (gCV%)
AUC_{0-24} [nM*h]	124 (20.4)	125 (33.1)
C_{max} [nM]	9.55 (39.3)	9.12 (50.2)
t_{max} [h]	2.00 (0.98-6.20)	1.50 (1.00-4.00)
$AUC_{\tau,ss}$ [nM*h]	148 (19.1)	187 (25.3)
$C_{max,ss}$ [nM]	12.3 (40.4)	15.3 (47.2)
$t_{1/2,ss}$ [h]	194 (15.1)	118 (26.2)
$R_{A,Cmax}$	1.29 (40.5)	1.68 (48.7)
$R_{A,\ AUC}$	1.20 (19.9)	1.49 (20.1)
Accumulation $t_{1/2}$ [h]	9.29	14.5 (36.7)

†interim-analysis
‡21 enrolled, only 20 were evaluable

Reviewer's comments
Small difference in linagliptin steady-state PK between Caucasian and African-American patients does not appear to be clinically relevant. No PD related differences were apparent between these ethnic groups.

Trial 1218.58 – evaluation of PK and PD of linagliptin in Chinese healthy subjects
PK of linagliptin following oral administration of 5 mg dose to healthy Chinese subjects is shown in Table 14. Single-dose and steady-state C_{max} and AUC for Chinese subjects were ~30% higher than that observed for Caucasian patients with T2DM (shown in Table 6 and Table 7). However, steady-state PK was comparable to that observed for African-Americans patients with T2DM (Table 13). As stated above for trial 1218.55, these higher exposures have been tested in Phase 2 and Phase 3 clinical trials for which there were no significant safety issues reported. DPP-4 inhibition was not measured and because of short duration of trial (7 days) HbA1c comparisons were not possible.

Table 14: Single-dose and steady-state PK for Chinese subjects (Trial 1218.58)

Trial	1218.58 (in Chinese†)
Linagliptin Dose	5 mg (N=12)
Parameter	gMean (gCV%)
AUC_{0-24} [nM*h]	150 (25.3)
C_{max} [nM]	10.4 (46)
t_{max} [h]	1.75 (1.50-8.00)
$AUC_{\tau,ss}$ [nM*h]	204 (24.5)
$C_{max,ss}$ [nM]	14.1 (49.4)
$t_{1/2,ss}$ [h]	103 (14.5)

$R_{A,Cmax}$	1.35 (38.3)
$R_{A,\ AUC}$	1.35 (17.8)
Accumulation $t_{1/2}$ [h]	11.5 (46.9)

†healthy subjects

Trials 1218.11 and 1218.12 – evaluation of PK and PD of linagliptin in Japanese healthy subjects and patients with type 2 diabetes, respectively

Trial 1218.11 evaluated single-dose and steady-state linagliptin PK in Japanese healthy subjects at dose levels 2.5 mg, 5 mg, and 10 mg. Following daily 5 mg doses of linagliptin, the geometric mean total exposure at steady-state ($AUC_{\tau,ss}$) was 193 nM·h (gCV: 24.5%) and the corresponding gMean maximum concentration ($C_{max,ss}$) was 12.0 nM (gCV: 49.4%). Geometric mean single dose exposure after the 5 mg dose, as measured by C_{max} and AUC_{0-24}, was 8.99 nM and 159 nM·h, respectively. These AUC values in Japanese subjects were approximately 25-30% higher than the values observed in Caucasian subjects (shown in Table 6 and Table 7). The plasma DPP-4 activity was inhibited in a dose-dependent manner with greater than 80% inhibition at trough was reached with doses of 5 mg and 10 mg linagliptin. The concentrations of linagliptin for 50% and 80% inhibition of DPP-4 enzyme were ~3 nM and ~4-6nM, respectively. These concentrations were comparable to the respective values of 2.97 nM and 5.30 nM for combined analysis of predominantly Caucasian data from trials 1218.2, 1218.3, 1218.5, and 1218.6.

The AUC and C_{max} values from trial 1218.12 evaluating linagliptin PK in Japanese patients with T2DM were also higher than that observed in Caucasian patients (Table 15). However, results from this trial should be interpreted with caution because several of these patients were receiving co-medications with potential to inhibit P-gp and CYP 3A4.

Table 15: Single-dose and steady-state PK for Japanese subjects (Trial 1218.12)

Trial	1218.12 (in Japanese patients with T2DM)		
Linagliptin Dose	0.5 mg (N=19)	2.5 mg (N=18)	10 mg (N=18)
Parameter	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)
AUC_{0-24} [nM*h]	29.9 (45.7)	129 (23.7)	323 (32.6)
C_{max} [nM]	2.81 (55.4)	8.84 (35.1)	35.1 (80.1)
t_{max} [h]	1.50 (1.0-2.0)	1.50 (0.5-8.0)	1.50 (0.5-12.0)
$AUC_{\tau,ss}$ [nM*h]	89.4 (27.2)	164 (23.4)	373 (33.5)
$C_{max,ss}$ [nM]	5.02 (33.9)	11.0 (40.9)	44.0 (80.4)
$t_{1/2,ss}$ [h]	240 (33.1)	223 (23.0)	260 (32.3)
$R_{A,Cmax}$	2.88 (28.3)	1.27 (21.4)	1.16 (27.8)
$R_{A,\ AUC}$	1.71 (35.8)	1.23 (40.4)	1.25 (78.0)

Reviewer's comments

The ~30% higher linagliptin exposures in Chinese and Japanese subjects compared to Caucasian subjects are not considered clinically meaningful in terms of impact on efficacy and safety.

2.3.1.4 Renal Impairment

Renal function affected linagliptin exposure as shown in Figure 36 based on results from a single-/multiple-dose PK study 1218.26. Linagliptin steady-state exposure (gMean) increased by 8% and 71% in non-diabetic subjects with mild and moderate renal impairment compared to that of non-diabetic subject with normal renal function (Table 16). In patients with T2DM, severe renal impairment group had 42% higher steady-state exposure (gMean) compared to normal renal function group (Table 16). On an average $AUC_{\tau,ss}$ were relatively higher for creatinine clearance <60 mL/min (Figure 37).

Comparison of AUC_{0-24} after single dose demonstrated 29%, 57%, 41%, and 54% increase in non-diabetic subjects with mild-, moderate-, severe-renal impairment and end stage renal disease, respectively, compared to non-diabetic subjects with normal renal function (Table 16). The PK parameters in these patients are summarized in Table 17. The accumulation factors ($R_{A,\,AUC}$ and $R_{A,\,Cmax}$) in T2DM patients with severe renal impairment were slightly higher compared to T2DM patients with normal renal function. The respective accumulation $t_{1/2}$ in these patients groups were 17.7 h and 13.6 h.

With observed 8 to 71% increase in exposure, sponsor proposed no dose adjustment for patients with renal impairment citing a broad safety profile of linagliptin.

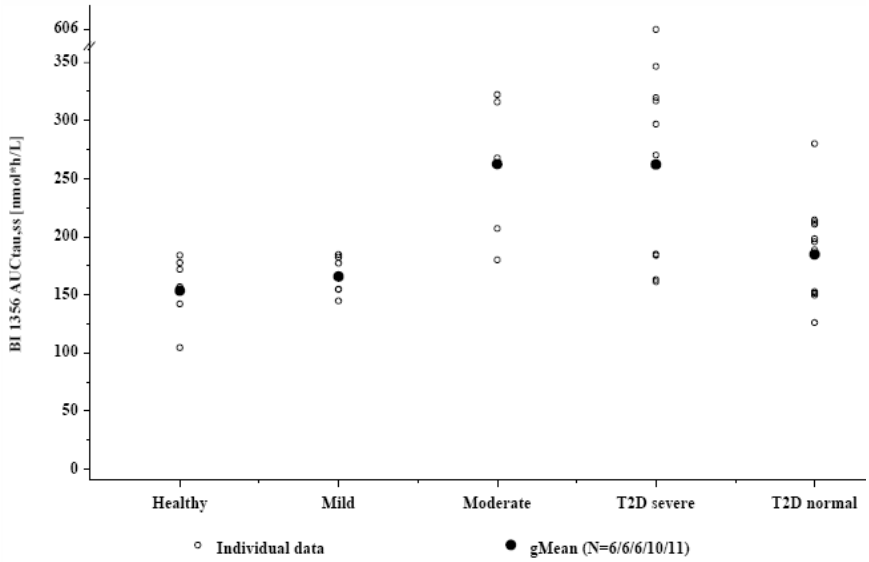


Figure 36: Steady-state AUC values of linagliptin (BI 1356) after oral administration of multiple 5 mg doses to subjects with normal renal function, patients with mild or moderate renal impairment, patients with T2DM and severe renal impairment, and patients with T2DM and normal renal function

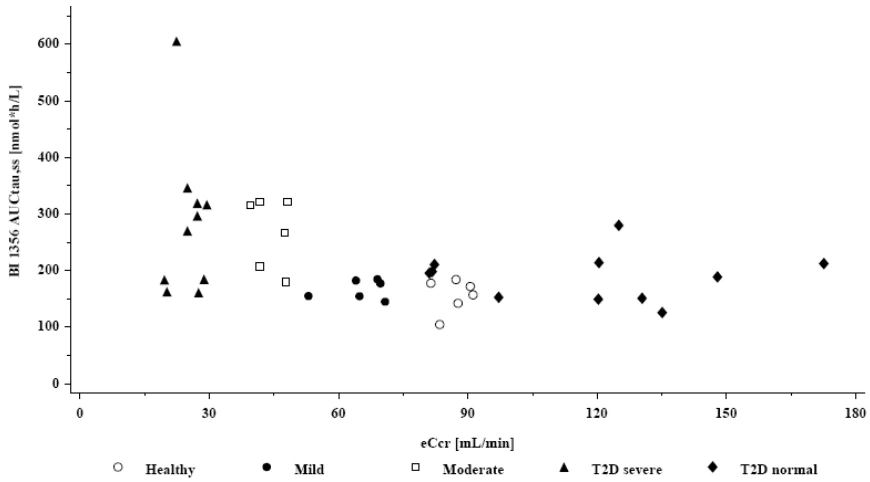


Figure 37: Scatter plot of CrCl (eCcr) and steady state $AUC_{\tau,ss}$ of linagliptin after oral administration of multiple 5 mg doses to subjects with normal renal function, patients with mild or moderate renal impairment, patients with T2DM and severe renal impairment, and patients with T2DM and normal renal function.

Table 16: Analysis of relative bioavailability of linagliptin after single and/or multiple oral administration of 5 mg linagliptin to renally impaired subjects or subjects with normal renal function

Linagliptin	Mildly impaired patients[1] (N=6)	Moderately impaired patients[1] (N=6)	Severly impaired patients[1] (N=6)	ESRD patients[1] (N=6)	Severely impaired T2DM patients[2] (N=10)
Parameter	Adjusted gMean ratio [T/R] [%] (90% CI) [%]	Adjusted gMean ratio [T/R] [%] (90% CI) [%]	Adjusted gMean ratio [T/R] [%] (90% CI) [%]	Adjusted gMean ratio [T/R] [%] (90% CI) [%]	Adjusted gMean ratio [T/R] [%] (90% CI) [%]
AUC_{0-24}	129.2 (100.7 - 165.7)	156.5 (105.8 - 231.5)	140.7 (103.9 - 190.5)	153.7 (117.9 - 200.4)	121.9 (92.0 - 161.6)
C_{max}	125.6 (80.4 - 196.3)	157.2 (77.4 - 319.2)	147.2 (83.2 - 260.7)	150.2 (93.5 - 241.4)	122.5 (81.5 – 184.0)
$AUC_{\tau,ss}$	107.9 (90.8 - 128.3)	170.8 (134.1 - 217.7)	---	---	141.8 (110.4 - 182.1)
$C_{max,ss}$	97.7 (70.2 - 135.9)	146.2 (97.6 - 218.9)	---	---	135.6 (96.6 - 190.1)

[1] compared to healthy controls (N=6)
[2] compared to T2DM patients with normal renal function (N=11)

Table 17: Geometric mean (%gCV) steady state noncompartmental PK parameters of linagliptin after oral administration of multiple 5 mg doses

Linagliptin		Control Healthy Subjects (N=6)	Mildly impaired patients (N=6)	Moderately impaired patients (N=6)	Control T2DM Patients (N=11)	Severely impaired T2DM Patients (N=10)
Parameter	[Unit]	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)
$AUC_{\tau,ss}$	[nM·h]	154 (21.2)	166 (10.3)	263 (25.6)	185 (22.8)	262 (43.8)
$C_{max,ss}$	[nM]	13.2 (38.9)	12.9 (24.5)	19.3 (41.3)	16.7 (32.1)	22.6 (60.8)
$t_{max,ss}$ [1]	[h]	0.517 (0.500-1.50)	2.50 (0.533-3.10)	1.27 (0.750-3.00)	1.00 (0.500- 3.00)	1.26 (0.750- 2.00)
$t_{1/2,ss}$	[h]	192 (31.4)	233 (17.6)	190 (32.5)	179 (47.2)	165 (56.6)
$Vz/F_{,ss}$	[L]	19000 (41.5)	20500 (22.2)	11000 (37.7)	14800 (66.9)	9630 (81.9)
$CL/F_{,ss}$	[mL/min]	1150 (21.2)	1060 (10.3)	672 (25.6)	954 (22.8)	673 (43.8)
$fe_{0-24,ss}$	[%]	4.26 (60.8)	3.71 (41.2)	4.03 (47.7)	6.45 (36.4)	2.68 (78.4)
$R_{A,Cmax}$		1.81 (37.4)	1.40 (28.3)	1.68 (63.8)	1.67 (30.2)	1.85 (31.2)
$R_{A,AUC}$		1.52 (15.6)	1.27 (14.1)	1.66 (31.9)	1.45 (18.3)	1.69 (22.5)

[1] Median (range)

Reviewer's comments

Sponsor's recommendation of no dose adjustment in patients with renal impairment is acceptable.

The 50-70% higher exposures of linagliptin in patients with moderate- or severe-renal impairment are acceptable without any dose adjustment because:

- safety of linagliptin in patients with renal impairment is being evaluated in a currently ongoing double-blind, placebo-controlled, Phase 3 efficacy and safety trial evaluating the linagliptin vs. placebo as add on to pre-existing antidiabetic therapy in type 2 diabetic patients with severe chronic renal impairment over 52 weeks (Trial # 1218.43). Based on 12-week interim analysis, no significant safety concerns were found in these patients.
- A higher dose of linagliptin 10 mg has been evaluated in a Phase 3 clinical trial in Japanese patients (Trial# 1218.23), for which the geometric mean of trough concentrations (i.e., C_{trough}) ranged from 8.07-8.92 nM. C_{trough} in patients with renal impairment (from renal impairment trial 1218.26 and safety and efficacy trial in patients with severe renal impairment 1218.43) were comparable or lower than the C_{trough} for 10 mg dose as shown in Figure 38. There were no significant safety issues that were identified in this trial. This suggests that safety of higher exposures, as observed in patients with renal impairment, has already been assessed and found acceptable.
- Additionally, we did not see any trend of increase in linagliptin trough concentrations with deteriorating renal function from moderate renal impairment to severe renal impairment. There were only few patients with end stage renal disease.

- Based on linagliptin disposition profile, its renal elimination is less than 5%. This provides further support that renal function will have a minor role in determining the linagliptin exposures.

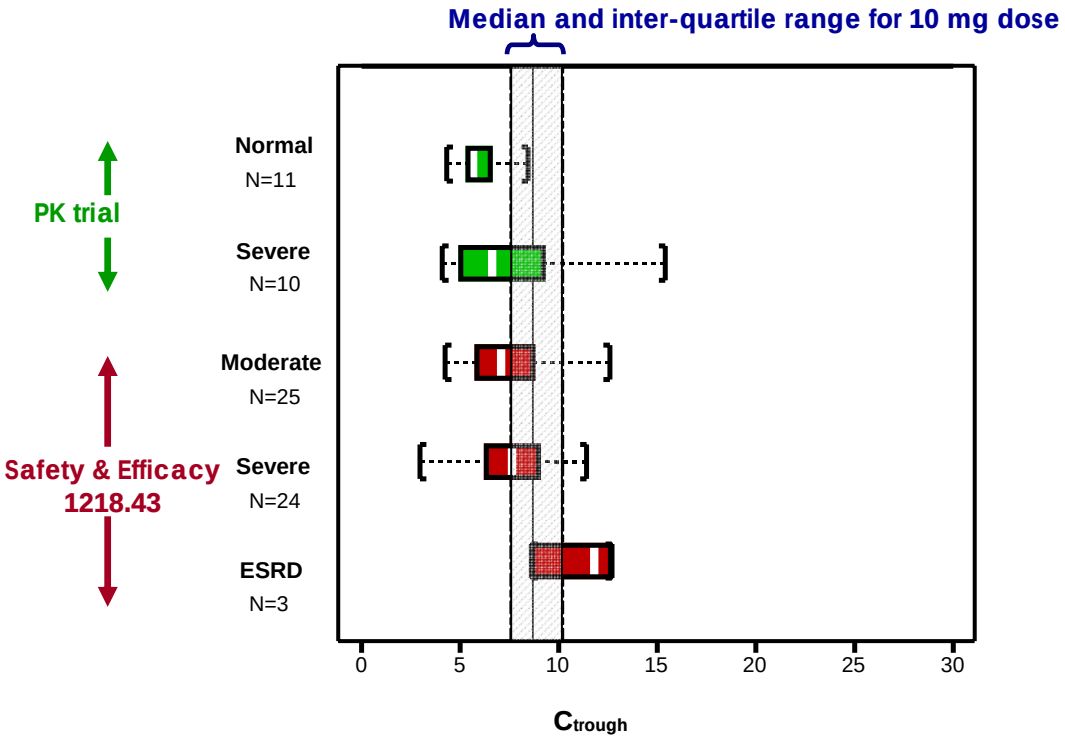


Figure 38: Box plot for comparison of trough concentrations in type 2 diabetic patients from PK renal impairment study 1218.26 and safety and efficacy trial in patients with renal impairment 1218.43. The shaded area shows the median and inter-quartile range for trough concentrations from 10 mg dose in Phase 3 trial in Japanese patients (# 1218.20)

2.3.1.5 Hepatic Impairment

Subjects with mild, moderate, and severe hepatic impairment had 13%, 22%, and 0% lower single-dose exposures (AUC_{0-24}) compared to healthy subjects. Steady-state exposures ($AUC_{\tau,ss}$) for mild and moderate hepatic impairment patients were 25% and 15% lower than the healthy subjects (Table 18). Reduction in C_{max} or $C_{max,ss}$ ranged from 8% to 36%. Most of these parameters had large variability resulting in wider 90% CI; however, most of these CI included 1, indicating no statistically significant difference between compared parameters (Table 18 and Table 19). Therefore, sponsor reported that the observed decrease in exposures were not clinically relevant.

Reviewer's comments

- Sponsor's conclusions suggesting no dose adjustments based on hepatic function is acceptable.
- Mechanistically, biliary excretion of unchanged parent drug is an important pathway of linagliptin elimination and the role of metabolism in linagliptin disposition is negligible.

- Note that concentrations of linagliptin 5 mg oral dose in healthy subjects in this trial were relatively higher than that observed in other clinical trials for the same dose (e.g., 1218.2, 1218.3). This difference could possibly be explained by small sample size.

Table 18: Analysis of relative bioavailability of linagliptin after single and/or multiple oral administration of 5 mg linagliptin to subjects with hepatic impairment or normal healthy subjects

Linagliptin	Mildly impaired patients[1] (N=8)	Moderately impaired patients[1] (N=8)	Severely impaired patients[1] (N=8)
Parameter	Adjusted gMean ratio [T/R] % (90% CI) [%]	Adjusted gMean ratio [T/R] % (90% CI) [%]	Adjusted gMean ratio [T/R] % (90% CI) [%]
AUC_{0-24}	86.8 (66.1-114.0)	78.2 (63.6-96.0)	100.4 (75.0-134.3)
C_{max}	68.8 (44.0-107.4)	70.0 (48.7-100.5)	77.0 (44.9-132.3)
$AUC_{\tau,ss}$	75.5 (61.6-92.5)	85.5 (70.2-104.2)	---
$C_{max,ss}$	64.4 (43.2-96.0)	92.3 (62.8-135.6)	---

[1]Compared to healthy controls (n=7)

Table 19: Key pharmacokinetic parameters of linagliptin after single and/or multiple oral administration of 5 mg linagliptin to hepatically impaired subjects or subjects with normal hepatic function

Linagliptin		**Control healthy subjects**	**Mildly impaired patients**	**Moderately impaired patients**	**Severely impaired patients[2]**
		(N=8)	(N=8)	(N=9)	(N=8)
Parameter	[Unit]	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)
$AUC_{\tau,ss}$	[nM·h]	254 (18.9)	191 (27.2)	217 (26.0)	190 (39.4) {233 (33,0)}
$C_{max,ss}$	[nM]	20.8 (38.6)	13.4 (55.8)	19.2 (52.5)	13.3 (77.8) {19.0 (67.0)}
$t_{max,ss}$[1]	[h]	1.50 (0.500-2.00)	1.00 (0.500-3.00)	0.625 (0.250-2.00)	0.875 (0.500-6.00)
$t_{1/2,ss}$	[h]	77.7 (32.6)	95.0 (18.0)	96.1 (54.7)	124 (61.2)
$Vz/F_{,ss}$	[L]	4680 (35.7)	7580 (38.4)	6760 (65.3)	1730 (33.4)
$CL/F_{,ss}$	[mL/min]	696 (18.9)	922 (27.2)	813 (26.0)	161 (38.5)
$fe_{0-24,ss}$	[%]	7.12 (50.3)	4.84 (57.8)	6.13 (51.2)	0.923 (275)
$R_{A,Cmax}$		1.20 (53.9)	1.22 (64.3)	1.53 (65.8)	---
$R_{A,AUC}$		1.34 (22.2)	1.25 (23.9)	1.46 (28.4)	---

[1] Median and range
[2] for the group with severe hepatic impairment single dose parameters are given. In addition model based predicted steady-state parameters are given {}.

2.3.1.6 Genetics

No pharmacogenetics information is available in this submission.

2.3.2 What pregnancy and lactation use information is there in the label?

There are no well-controlled studies evaluating linagliptin in pregnant or lactating women. Therefore, it should only be used only if clearly needed. Only preclinical reproduction studies have been performed in rats and rabbits. Please refer to pharmacology/toxicology review by Dr. David Carlson for detailed assessment of preclinical teratogenic effects of linagliptin.

2.4 Extrinsic Factors

2.4.1 What are the drug-drug interactions?

2.4.1.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Drug-drug interaction of linagliptin based on induction or inhibition of CYP enzymes is less likely at therapeutic concentrations. Please see sections 2.4.1.2 and 2.4.1.3.

2.4.1.2 Is the drug a substrate of CYP enzymes?

Yes, linagliptin is substrate of CYP enzymes. CYP3A4 was the main human isoform metabolizing linagliptin and there was no indication for a contribution of other CYP enzymes based on *in vitro* experiments with expressed human CYPs. The predominant human metabolite is CD1790 (amino function of piperinidyl moiety was substituted by hydroxy group, M474(1) in Figure 24). Formation of other metabolites was very low. Ketoconazole inhibited the formation of oxidative metabolites including CD1790, confirming that these metabolites were formed by CYP3A4.

2.4.1.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Induction

Linagliptin is not an inducer of hepatic cytochrome P450. No indications on biologically relevant changes of cytochrome P450 activity were observed in rats after repeated once daily oral administration of 6 or 60 mg/kg linagliptin for 4 days. There were no indications of induction of hepatic enzymes CYP1A2, 2B6, and 3A4 by linagliptin in *in vivo* rat studies and *in vitro* experiments with cultured human hepatocytes.

Inhibition

Linagliptin weakly inhibited CYP 3A4 activity in human liver microsomes in a competitive manner with a Ki of 115 μM and mono amino oxidase B (MAO-B) catalysed kynuramine deamination with a Ki of 2.39 μM. Additionally, linagliptin was found to be a poor to moderate mechanism-based (irreversible) inhibitor of CYP 3A4 in human liver microsomes (k_{inact} = 0.027 min^{-1} to 0.041 min^{-1}). Considering the therapeutic plasma concentrations of linagliptin in the low nanomolar range, a clinical relevance of this finding is unlikely. There was no inhibition of the other studied CYP isoenzymes by linagliptin (Cytochromes 1A2, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11).

CD 1790 was found to be a competitive inhibitor of CYP 2C9 and a mechanism-based inhibitor of CYP 3A4 in *in vitro* human liver microsome studies. The IC50% values for inhibition of CYP 2C9 and CYP3A4 were in the range of 8.28 to 25.2 μM. Considering that maximum plasma concentrations of CD 1790 are in the nM range, a clinically relevant CYP 2C9 mediated interaction is unlikely.

2.4.1.4 Is the drug a substrate and/or an inhibitor/ inducer of P-gp transport processes?

Linagliptin appears to be a substrate and a weak-inhibitor of P-gp (Table 20). In the concentration range between 0.3 and 300 μM, apparent a-b permeability coefficient increased and apparent b-a permeability coefficient decreased for linagliptin's apically directed vectorial transport in a concentration dependent manner. P-gp inhibitors verapamil (200 μM) and cyclosporin (12 μM) almost completely abolished the vectorial transports of linagliptin while the MRP inhibitor MK571 exerted only a minimal effect, suggesting that linagliptin is a P-gp substrate.

The presence of linagliptin (0.3 - 300 μM) resulted in a concentiation dependent and saturable inhibition of the P-gp mediated efflux of digoxin, suggesting that linagliptin is an inhibitor of P-gp. The apparent IC_{50} for P-gp inhibition was 55μM, indicating to a lower potency of linagliptin for P-gp inhibition.

2.4.1.5 Are there other metabolic/transporter pathways that may be important?

Among efflux transporters other than P-gp, linagliptin was not a substrate or an inhibitor for BCRP and MRP2 transporters (Table 20).

Evaluation of linagliptin as a substrate and/or inhibitor of SLC uptake transporters revealed that linagliptin was a substrate for OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2, suggesting a possible OATP8-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and reabsorption of linagliptin *in vivo*.

OATP2, OATP8 and OCTN1 activities were slightly inhibited by linagliptin at the highest concentration of 100 μM (Table 20). Additionally, OCT1 and OATP2 activities were significantly inhibited with IC_{50} values of 45.2 μM and 69.7 μM, respectively (Table 20). Given the micromolar concentrations of linagliptin that are needed for inhibition of the denoted SLC transporters a clinical DDI is very unlikely.

In a further study in porcine kidney epithelial cell line LLC-PK1 it was demonstrated, that active secretion of linagliptin in the kidney may occur, which is in line with renal clearance values of linagliptin exceeding the glomerular filtration rate in humans at high, supratherapeutic doses (up to 600 mg). Additionally, high affinity and low capacity binding of linagliptin to a protein was suggested by saturation of the total transport clearance in this cell line.

Table 20: Linagliptin as substrate or inhibitor for transporters

Transporter family	Transporter	Linagliptin as substrate	Linagliptin as inhibitor	IC_{50}
ABC	MDR1 (P-gp)	Yes (Km=187 µM)	Yes	55 µM
	BCRP	No	No	
	MRP2	No	No	
SLC	OATP8	Yes	Yes	>100 µM
	OCT2	Yes	No	
	OAT4	Yes	No	
	OCTN1	Yes	Yes	>100 µM
	OCTN2	Yes	No	
	OATP2	No	Yes	69.7 µM
	OATP-B	No	No	
	OCT1	No	Yes	45.2 µM
	OAT1	No	No	
	OAT3	No	No	

2.4.1.6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Drug interaction was evaluated as follows and the results are summarized in Table 21 and Table 22:

- Effect of linagliptin on PK of co-administered drugs: Simvastatin, Digoxin, Warfarin, Metformin, Microgynon®, Pioglitazone, and Glyburide
- Effect of co-administered drugs on linagliptin PK: Ritonavir, Rifampicin, Metformin, Pioglitazone, and Glyburide

Table 21: Effect of linagliptin on co-administered drugs

Linagliptin Regimen	**Substrate**	**GMR (90% CI)**	
		AUC	**C_{max}**
Linagliptin 10 mg QD (days 7-12)	**Simvastatin**† (CYP 3A4 substrate) 40 mg QD (monotherapy days 1-6, co-administered with linagliptin days 7-12, monotherapy days 13-20)	**1.34** (1.19-**1.51**)	1.10 (0.89-**1.35**)
	Simvastatin acid†	**1.33** (1.18-**1.50**)	1.20 (1.02-**1.44**)
Linagliptin 5 mg QD (Arm B: days 1-12)	**Warfarin** (CYP 2C9 substrate) 10 mg QD (Arm A: day 1; Arm B: co-administered with linagliptin on day 6)		
	R-warfarin	0.99 (0.96-1.01)	1.00 (0.95-1.05)
	S-warfarin	1.02	1.01

		(0.99-1.07)	(0.94-1.09)
	INR‡	0.93 (0.86-1.01)	1.04 (0.85-**1.27**)
	PT‡	1.03 (0.95-1.12)	1.15 (0.94-**1.41**)
Linagliptin 5 mg QD (Arm A: co-administration with digoxin on days 6-11)	**Digoxin**† (P-gp substrate) 0.25 mg QD (Arm A: monotherapy on days 1-6 and co-administration with linagliptin on days 6-11; Arm B: days 1-11)	1.01 (0.97-1.06)	0.94 (0.87-1.03)
Linagliptin 5 mg QD (co-administered with Microgynon® on days 15-21)	**Microgynon**® (30 µg ethinylestradiol (EE) + 150 µg levonorgestrel (LNG)) (monotherapy on days 1-14 and co-administration with linagliptin on days 15-21)		
	EE	1.01 (0.97-1.06)	1.08 (1.00-1.17)
	LNG	1.08 (1.04-1.13)	1.14 (1.06-**1.21**)
Linagliptin 10 mg QD (Arm B: monotherapy on days 1-6 followed by co-administration with metformin for days 7-9)	**Metformin**† (OCT substrate) 850 mg TID (Arm A: as monotherapy on days 1-3; Arm B: co-administered with linagliptin on days 7-9)	1.01 (0.89-1.14)	0.89 (**0.78**-1.00)
Linagliptin 10 mg QD (Arm A: monotherapy on days 1-5 and continued to Arm B: co-administered with pioglitazone on days 6-12)	**Pioglitazone**† (CYP2C8 and CYP3A4 substrate) 45 mg QD (Arm B: co-administered with linagliptin on days 6-12; Arm C: monotherapy on days 1-7)	0.94 (0.87-1.02)	0.86 (**0.78**-0.94)
Linagliptin 5 mg QD (Arm A: monotherapy on days 1-5 and continued to Arm B: co-administered with glyburide on day 6)	**Glyburide** (CYP2C9 substrate) 1.75 mg (Arm B: single-dose co-administered with linagliptin on day 6; Arm C: single-dose on day 1)	0.86 (0.80-0.92)	0.86 (0.80-0.93)

†Based on assessment of steady-state PK
‡PD endpoints (INR-international normalization ratio; PT-prothrombin time)
Bolded values indicate deviation from BE criteria.

Table 22: Effect of co-administered drugs on linagliptin

Co-administered drug	Linagliptin	GMR (90% CI)	
		AUC	C_{max}
Ritonavir (potent P-gp and CYP3A4 inhibitor) 200 mg BID (test arm: days -1 to 2)	Linagliptin 5 mg QD (test arm: co-administered with	**2.01** (**1.86**-**2.18**)	**2.96** (**2.52**-**3.47**)

	ritonavir on day 1; reference arm: single-dose on day 1)		
Rifampicin† (potent P-gp and CYP3A4 inducer) 600 mg QD (monotherapy on days -1 to -6 followed by co-administration with linagliptin on days 1 to 6)	Linagliptin 5 mg QD (co-administered with rifampicin on days 1 to 6)	**0.61** (**0.56**-**0.66**)	**0.56** (**0.48**-**0.66**)
Metformin† 850 mg TID (Arm A: as monotherapy on days 1-3; Arm B: co-administered with linagliptin on days 7-9)	Linagliptin 10 mg QD (Arm B: monotherapy on days 1-6 followed by co-administration with metformin for days 7-9)	1.20 (1.07-**1.34**)	1.03 (0.86-**1.24**)
Pioglitazone† 45 mg QD (Arm B: co-administered with linagliptin on days 6-12; Arm C: monotherapy on days 1-7)	Linagliptin 10 mg QD (Arm A: monotherapy on days 1-5 and continued to Arm B: co-administered with pioglitazone on days 6-12)	1.13 (1.03-**1.25**)	1.07 (0.92-**1.25**)
Glyburide† 1.75 mg (Arm B: single-dose co-administered with linagliptin on day 6; Arm C: single-dose on day 1)	Linagliptin 5 mg QD (Arm A: monotherapy on days 1-5 and continued to Arm B: co-administered with glyburide on day 6)	1.02 (0.98- 1.06)	1.01 (0.89-1.14)

†Based on assessment of steady-state PK

Bolded values indicate deviation from BE criteria.

Based on results shown above sponsor recommended no dose adjustments for linagliptin or any co-administered drug.

Reviewer's comments

1. Mean increase in simvastatin and simvastatin acid AUC by 34% and 33% depicts weak inhibition of CYP3A4 and is not considered clinically relevant
2. Slight deviations in AUC and C_{max} of warfarin, digoxin, Microgynon® (ethinylestradiol and levonorgestrel), metformin, pioglitazone, and glyburide were not considered clinically relevant
3. Co-administration of ritonavir with linagliptin, increased linagliptin AUC_{0-24} by 101% and C_{max} by 196%. Following co-administration AUC_{0-24} values increased to 246 nM.hr. Sponsor performed simulations to predict the geometric mean of $AUC_{\tau,ss}$ for linagliptin 5 mg dose when co-administration with ritonavir, which was 293 nM.hr. Despite of this ~2-fold increase in exposure this reviewer is not recommending any dose adjustment because: (a) exposures as high as almost double the exposure of 5 mg dose has been evaluated in a 52-week long-term safety and efficacy trial (Trial # 1218.23) evaluating 10 mg dose as discussed under section 2.3.1.4, and (b) a higher 10 mg dose has also been tested in Phase 2 trials of up to 12 weeks duration (Trials # 1218.5 and 1218.6). There were no significant safety issues identified in these Phase 2 and Phase 3 trials. Please refer to clinical review for results of safety analysis from

Phase 3 trials. Additionally, doses up to 600 mg have been found to be safe in single-dose study (Trial # 1218.1). Therefore, sponsor's recommendation for no dose adjustment is acceptable.

4. Co-administration of rifampin with linagliptin, decreased linagliptin $AUC_{\tau,ss}$ by 39% and $C_{max,ss}$ by 44%. The resulting linagliptin $AUC_{\tau,ss}$ value was 87.6 nM·hr (range 66-114 nM·hr). This exposure was close to the exposure observed for 1 mg dose (i.e., 81.7 nM·hr, (range 51-114 nM·hr), Table 6), which based on results of trial 1218.6 (see Figure 8 in section 2.2.2) was subtherapeutic. Therefore, efficacy of linagliptin will be reduced in patients taking linagliptin with CYP 3A4 and P-gp inducers. This reviewer recommends the following to be added in linagliptin label: we strongly recommended use of alternative treatments when linagliptin is to be co-administered with P-gp or CYP 3A4 inducers.

5. Co-administration of metformin, glyburide, and pioglitazone with linagliptin did not have any clinically relevant effect on linagliptin exposures.

2.4.1.7 Is there *in vivo* chiral conversion of the drug? How is it addressed?

Yes, linagliptin has one chiral center (see the chemical structure in Figure 5). The R-enantiomer is used as the active ingredient. In human plasma, following single oral administration of 600 mg linagliptin, only the parent compound with R-configuration was identified using a validated enantio-selective HPLC-MS/MS method. The enantiomeric excess of the R-enantiomer accounted for (b) (4) in humans.

On the contrary, for the main metabolite of linagliptin (i.e., CD1790), only the S-configuration was identified.

These results suggest that there was negligible chiral inversion of linagliptin *in vivo* in humans, if at all present, and that the formation of the corresponding S-configured alcohol CD 1790 was highly stereo selective.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Linagliptin can be considered a BCS class 3 drug because of high aqueous solubility and moderate permeability.

Solubility: Linagliptin shows high solubility in aqueous media over the entire physiological pH-range (> 1 mg/mL up to pH 8.0). At pH>8 solubility of linagliptin is reduced due to its basic property (approx. 0.6 mg/mL at pH > 8). Linagliptin's solubility in water is 0.9 mg/mL. Since linagliptin's solubility in all pHs is greater than 0.02 mg/mL (highest tablet strength, 5 mg in 250 mL), linagliptin can be considered *highly soluble* based on the BCS guidance.

Permeability: Linagliptin has moderate permeability as determined based on comparison to the reference compounds mannitol (low permeability), atenolol (medium permeability) and propranolol (high permeability) observed in Caco-2 cells (intrinsic passive permeability of linagliptin 3.56 x 10^{-6} cm/s [mean ± 33.3% CV, N = 12]; mannitol 5.38 x 10^{-7} cm/s [mean ± 8.2% CV, N=3]; atenolol 1.21 x 10^{-6} cm/s [mean ± 12.2% CV, N=3]; propranolol 2.01 x 10^{-5} cm/s [mean ±3.0%, N = 3]). Linagliptin's oral systemic bioavailability is about 30% compared to intravenous (i.v.) administration despite of negligible metabolism. These data show that linagliptin does not qualify into a highly permeable drug based on the BCS classification.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulations?

The final formulation differs from the intended final formulation (iFF, used in all Phase 3 efficacy and safety trials as well as in some Phase 1 and 2 trials) (b) (4) . Sponsor states that these minor differences (b) (4) are not considered relevant for the *in-vivo* performance. Please refer to ONDQA review for the evaluation of this claim.

For the initial clinical studies, a linagliptin powder in the bottle (PIB) and uncoated tablet formulation (trial formulation 1 [TF-1]) were used. The powder in the bottle formulation covered a low dose strength of 5 mg and a high dose strength of 100 mg (for bridging purposes with the tablet formulation administered at the same dose level [2x50 mg]), whereas the tablets covered the dose strengths of 25 mg, 50 mg and 200 mg. Since a therapeutic dose 10-100 fold lower than what was previously projected was anticipated, development of TF-I was discontinued and a 40 mg oral drinking solution (reconstitution with 0.1% tartaric acidic) was developed for a 2 week multiple rising dose study. Further a low dose tablet trial formulation II (TF-II) was developed at strengths of 1 mg, 2.5 mg, 5 mg and 10 mg and used in the 4 week MRD trial. TF II was further optimized to improve tablet stability resulting in trial formulation IIb (TF-IIb). And finally a film-coated tablet formulation (intended final formulation [iFF]) was developed on the basis of TF-IIb. Relative bioavailability of these formulations was compared in trials 1218.8 and 1218.25. These trials demonstrated the bioequivalence among these formulations (1 mg and 10 mg formulation in trial 1218.8 and 5 mg formulation in trial 1218.25) with geometric mean ratios for AUC and C_{max} in the range of 0.8 to 1.25.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

The results in Table 23 demonstrate no change in extent of absorption following linagliptin's administration immediately after a high fat, high caloric breakfast compared to fasting state. However, maximum plasma concentrations were reduced in the fed studies arms by about 25% and 15%. For the proposed to-be-marketed strength of 5 mg a

15% reduction in C_{max} was observed, which is not considered clinically relevant. Sponsor proposes that linagliptin can be administered without restriction on food.

Table 23: Comparison of linagliptin PK parameter ratios (point estimator and 90% CI) from food interaction trials in healthy subjects (trials 1218.8, 1218.34)

Trial	N	Test	Reference	Parameter	Geometric mean ratio	Lower 90% CI [%]	Upper 90% CI [%]	Intraind. gCV [%]
1218.8	12/12	10 mg tablet fed (TF-II)	10 mg tablet fasted (TF-II)	$AUC_{0-\infty}$	95.8	90.3	101.6	8.4
				C_{max}	75.1	60.7	92.8	30.8
1218.34	32/31	5 mg tablet fed (iFF)	5 mg tablet fasted (iFF)	AUC_{0-72}	103.5	98.1	109.2	12.4
				C_{max}	84.7	75.9	94.6	26.1

Reviewer's comments
Sponsor's recommendation that linagliptin can be administered in fed or fasted state is acceptable.

2.6 Analytical Section

2.6.1 What bioanalytical methods were used to assess concentrations of linagliptin and/or metabolite?

Measurement of linagliptin and its metabolite CD 1790 in biological metrics plasma and urine was performed with validated HPLC-MS/MS methods. The reference standard for linagliptin was linagliptin itself and for CD 1790 it was CD 1750 (a racemic mixture).

Plasma was mixed with acetic acid/acetonitrile containing the isotope labelled internal standards [$^{13}C_3$] BI 1356 BS and [$^{13}C_3$] CD 1750 XX and samples were cleaned up by solid phase extraction (SPE) in the 96-well plate format. Chromatography was achieved on an analytical (b) (4) phase HPLC column with gradient elution. The substances were detected by HPLC-MS/MS in the positive electrospray ionization mode. A similar process was used for analysis of urine samples.

2.6.2 Which metabolites have been selected for analysis and why?

Metabolite CD 1790 was analyzed in clinical studies because it was the predominant metabolite of linagliptin.

2.6.3 For all moieties measured, is free, bound, or total measured?

Total plasma concentrations were measured for all moieties.

2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The range of standard curve for linagliptin measurement in plasma was 0.100 to 100 nmol/L and for CD 1790 it was 0.0500 to 50.0 nmol/L using a plasma volume of 150 µL.

The calibration curves were fitted by the equation $y = a + bx$ with a weighting factor of $1/x^2$. For analysis of highly concentrated samples, sample dilution was performed.

2.6.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ and ULOQ for linagliptin were 0.100 nmol/L and 100 nmol/L, respectively. For CD 1790 these values were 0.0500 nmol/L and 50 nmol/L, respectively.

2.6.6 What are the accuracy, precision, and selectivity of this assay method?

The accuracy and precision for determination of linagliptin and CD 1790 in plasma are greater than 90% and for determination of these molecules in urine these parameters are greater than 86%. No interference from endogenous compounds was reported for determination of linagliptin and CD 1790.

2.6.7 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, autosampler etc.)?

Linagliptin and CD 1790 have been demonstrated to be stable in stock solution for a minimum of 9 days, up to two freeze-thaw cycles, up to 24 hours at room temperature, for up to 13 months at -20 °C, and up to 66 hours in the autosampler at +12 °C.

2.6.8 What QC concentrations were used for sample analysis?

The QC concentrations for linagliptin analysis were 0.250, 5, and 80 nmol/L and for dilution analysis it was 400 nmol/L. The QC concentrations for analysis of CD 1750 in human plasma are 0.250, 5, and 80 nmol/L.

2.7 Detailed Labeling Recommendations

Following are the labeling comments for the sponsor.

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the population pharmacokinetic analysis support the sponsor's proposed labeling claims regarding the effects of body weight, age, gender, and ethnicity?

Body weight, age, and gender did not have any significant effect on linagliptin exposure. Please see section 2.3.1.1 for more details. With limited number of patients of African-American, Hispanic, and Asian race, no significant difference in linagliptin exposure was observed between these groups. However, there were other supportive evidences to support no dose adjustment based on ethnicity. Please see section 2.3.1.3 for more details.

1.1.2 Does the dose-response or exposure-response analysis support the selection of 5 mg dose?

Yes, we agree with sponsor's selection of 5 mg dose. However, sponsor could have also further evaluated the 2.5 mg dose. Please see section 2.2.2 for more details.

1.2 Recommendations

No linagliptin dose adjustments are required based on covariates body weight, age, gender, and ethnicity.

1.3 Label Statements

Please check the detailed labeling recommendations in section 2.7.

2 Results of Sponsor's Analysis

Per sponsor, the primary objective of population PK analysis was to investigate the impact of demographic factors, concomitant therapies, and laboratory covariates on the PK of linagliptin.

2.1 Data Sets Used For Model Development

Plasma samples from the following studies were used in the analysis:

A. Phase 1 trials 1218.2 and 1218.3:

In these trials, a complete PK profile was collected after the first and the last administration of linagliptin, in between just trough values were sampled. As linagliptin has a long terminal half-life, samples were collected until 8 and 15 days after the last administration of linagliptin in the 1218.2 and 1218.3 trials, respectively (see Table 24 and Table 25).

Table 24: PK sampling time points in study 1218.2

Day	Parameter	Time
1	BI 1356	before and 0:30 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 hours after first administration
2-11		before every BI 1356 administration
	BI 1356	and as well as one night sampling on day 11 (18 h after drug administration of day 10)
12	BI 1356	before, 0:30 h, 1 h, 1:30 h, 2h, 3 h, 4 h, 6 h, 8 h, and 12 hours after last administration
13, 14, 16, 18, 20	BI 1356	in the morning

Source: Report on Combined Population Pharmacokinetic Analysis for Linagliptin (pg 121)

Table 25: PK sampling time points in study 1218.3

Day	Parameter	Time
1	BI 1356	before and 0:30 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 hours after first administration
2, 6, 12, 19, 26, 27	BI 1356	before every BI 1356 administration and as well as one night sampling on day 27 (18 h after drug administration of day 10)
28	BI 1356	before, 0:30 h, 1 h, 1:30 h, 2h, 3 h, 4 h, 6 h, 8 h, and 12 hours after last administration
29, 30, 33, 36, 39, 41, 43	BI 1356	in the morning

Source: Report on Combined Population Pharmacokinetic Analysis for Linagliptin (pg 121)

B. Phase 2b trials 1218.5 and 1218.6:

Linagliptin plasma concentrations were measured at 4 occasions (visits 4, 6, 7 and 8) - always before and 1h (+/- 0.5 h) and 2h (+/- 1 h) after linagliptin administration and in addition one sample was taken at follow up visit 9 (see Table 26).

Table 26: PK sampling time points in studies 1218.5 and 1218.6

Visit	Parameter	Time
4, 6, 7, 8	BI 1356	before and 1 h (+/- 0.5 h), 2 h (+/- 1 h) after administration
9	BI 1356	One sample at any time during the end of trial visit

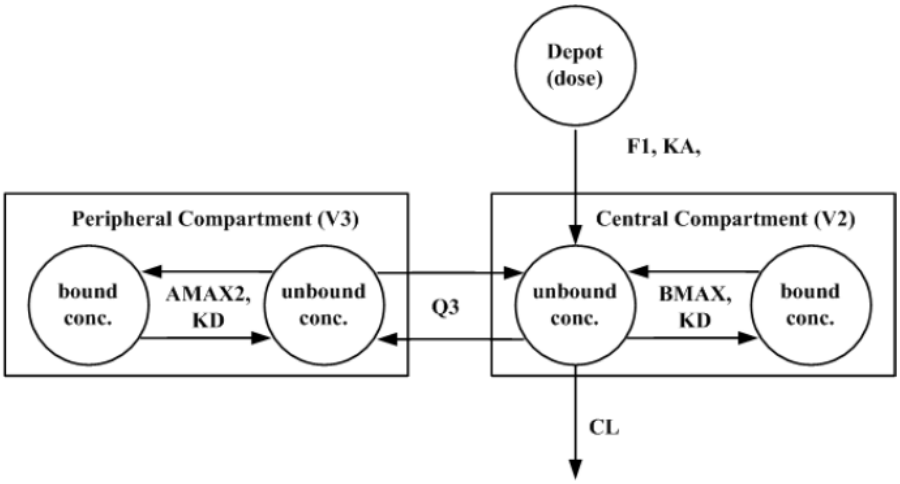
Source: Report on Combined Population Pharmacokinetic Analysis for Linagliptin (pg 122)

2.2 Model Development

A semi-mechanistic model was initially developed based on data from Phase 1 trials. The nonlinear PK of linagliptin was described assuming concentration dependent protein binding of linagliptin to its target DPP-4. This model was further adjusted to fit the data from all 4 Phase 1 and Phase 2 trials. The final model is shown in Figure 39.

2.2.1 Population PK model

- Model structure: two-compartment disposition model with concentration dependent protein binding of linagliptin in central and peripheral compartments
- Residual error model (σ): Additive error model
- Inter-individual (ω) and inter-occasion (κ) random effects: Inter-subject variability on F1, KA, BMAX, V2, and CL and inter-occasion variability on F1 were included to describe the variability in the plasma concentration time profiles. IIV and IOV were both modeled using exponential random effect models.



Legends:
F1, bioavailability; KA, absorption rate constant; BMAX, concentration of binding sites in the central compartment; KD, affinity constant; V2, central volume of distribution; V3, peripheral volume of distribution; Q3, intercompartmental clearance between central and peripheral compartment; AMAX2, amount of binding sites in the peripheral compartment; CL, clearance

Figure 39: Structure of the base PK model

Source: Report on Combined Population Pharmacokinetic Analysis for Linagliptin (pg 40)

The goodness-of-fit plots from the base PK model are shown in Figure 40 and the parameters are listed in Table 27. Because of long run time covariance step was not included in the base model; therefore, %RSE and 95%CI are not reported.

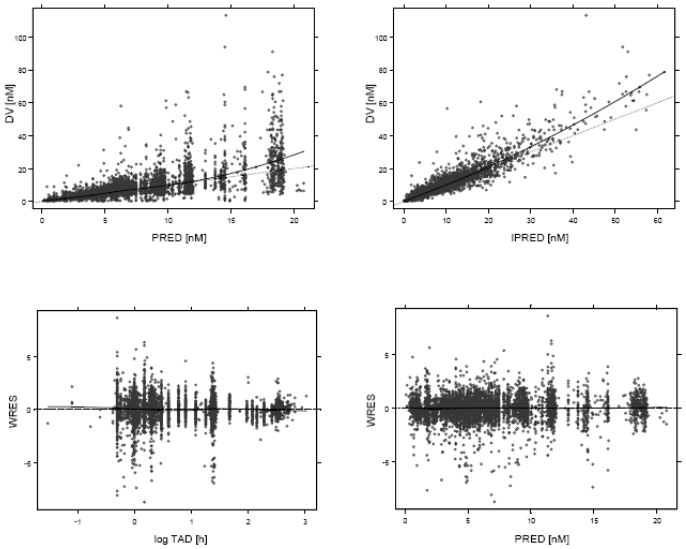


Figure 40: Basic goodness-of-fit plots for the base PK model

Reviewer's Comment

The goodness of fit plots indicate an adequate performance of the model to describe linagliptin pharmacokinetics

Table 27: Parameter estimates of the base PK model

Parameter	Value		Description
Fixed effects			
F1 [%]	100	FIX	Typical absolute bioavailability
F1 in study 1218.6 [%]	151		Typical absolute bioavailability in study 1218.6 relative to F1
KA [1/h]	0.549		Typical absorption constant
V2/F1 [L]	713		Typical central volume of distribution
Q3/F1 [L/h]	412	FIX	Typical inter-compartmental clearance between central compartment and peripheral compartment 1
V 3/F1 [L]	1650	FIX	Typical volume of distribution of the peripheral compartment 1
CL/F1 [L/h]	243		Typical clearance of the unbound concentration
BMAX [nmol/L]	4.82		Typical concentration of binding sites in the central compartment
KD [nmol/L]	0.0652	FIX	Typical affinity constant of the nonlinear binding
AMAX2/F1 [nmol]	1650	FIX	Typical amount of binding sites in the peripheral compartment 1

Table 27: Parameter estimates of the base PK model (cont.)

Parameter	Value	Description
random effects		
IIV_F1 [CV%]	44.2	Inter individual variability in the absolute bioavailability
Cor_F1_CL	-0.704	Correlation between IIV_F1 and IIV_CL
IIV_CL [CV%]	23.9	Inter individual variability in the clearance of the unbound concentration
IIV_KA [CV%]	87.6	Inter individual variability in the absorption constant
IIV_V2 [CV%]	22.6	Inter individual variability in the central volume of distribution
IIV_BMAX [CV%]	29.6	Inter individual variability in the concentration of central binding sites
IOV_F1 [CV%]	39.2	Intra individual variability in the absolute bioavailability
prop. residual variability [%]	13.6	Residual variability Phase I
prop. residual variability [%]	38.1	Residual variability Phase IIb

2.2.2 Covariate model

Twenty-six covariates were tested for their influence on the parameters F1, KA, V2, CL, and BMAX. Covariates were selected based on: (a) the correlation between covariates and individual parameter estimates (exploratory analysis) and (b) the results of the GAM analyses. Correlation between covariates was also considered when selecting the covariates. In addition some covariates were pre-selected to be tested in NONMEM, independent on the results of the exploratory analysis or GAM analysis to assure that shrinkage does not hide the covariate selection for these most important covariates.

- All covariates which were significant in the initial analysis based on trials 1218.2 and 1218.3 (i.e., PROJ on F1, DOSE on KA, ALT on CL, AST on BMAX). Where, PROJ-is a categorical variable referring to four trials, ALT refers to alanine transaminase levels, and AST refers to aspartate transaminase levels.
- Due to special interest in the patient population:
  - CRCL and the liver enzymes ALT, GGT and AP were selected to be tested on CL and WT on V2. Where, CRCL was creatinine clearance and AP referred to alkaline phosphatase levels.
  - AGE, WT, SEX were pre-selected to be tested within NONMEM on all model parameters with IIV.

Covariates were added by forward addition and backward elimination procedure, which was performed separately per model parameter. All selected covariates were tested together in one run. Following which a stepwise backward elimination was performed. Based on these results, weight on the apparent central volume of distribution was not included in the final model, because weight was already implemented on the bioavailability and therefore it was not additionally needed on V2.

The covariates were considered clinically relevant if the AUC changed more than ±25% between typical and either of the extreme covariate values (5th and 95th percentiles of covariate distribution for continuous covariates). Only one covariate was assessed at a time.

Individual influence of each covariate on $AUC_{\tau,ss}$ is summarized in Table 28. None of the statistically significant covariates were clinically relevant. The combination of all covariates in two worst-case scenarios, i.e., **(a)** an old (73 years), low-weight (67 kg), female patient on metformin medication with high GGT (158 U/L) and high pre-dose DPP-4 activity (18623 RFU), or, **(b)** a young (42 years), high-weight (117 kg), male patient with low GGT (9.4 U/L), low pre-dose DPP-4 activity (8025 RFU), and on linagliptin monotherapy resulted in 26% decrease and 38% increase in $AUC_{\tau,ss}$, respectively.

Reviewer's comment

For the above mentioned worst case scenario (b) sponsor reported a change in $AUC_{\tau,ss}$ by +63%. However, in our analysis this value came out to be +38%. Either of these exposures will not be considered unsafe given that almost two fold higher exposures have been tested in Phase 3 trial 1218.23.

Table 28: Covariate influence on $AUC_{\tau,ss}$ after administration of 5 mg linagliptin

Model parameter	Statistically significant covariate	Categories	Typical $AUC_{\tau,ss}$ [nM*h]	%difference from median
F1	Metformin comedication	No	154.23	
		Yes	184.81	+19.8%
	WT	P.05 (67 kg)	163.38	+5.9%
		Median (88 kg)	154.23	
		P.95 (117 kg)	140.9	-8.7%
BMAX	AGE	P.05 (42 years)	142.8	-7.4%
		Median (60 years)	154.23	
		P.95 (73 years)	162.5	+5.4%
	SEX	Male	154.23	
		Female	164.65	+6.8%
	DOSE	0.5	136.8	-11.3%
		5	154.33	
		10	173.6	+12.5%
	DPP	P.05 (8025 RFU)	137.4	-10.9%
		Median (12497 RFU)	154.23	
		P.95 (18623 RFU)	177.3	+15.0%
KA	FORM	1	153.66	-0.4%
		2	153.75	-0.3%
		3	154.23	
	DOSE	0.5	153.99	-0.2%
		5	154.23	
		10	154.67	+0.4%
CL	GGT	P.05 (9.4)	153.84	-0.25%
		Median (33)	154.23	

	P.95 (158)	156.38	+1.4%

The final model parameters and goodness-of-fit plots are displayed in Table 29 and Figure 41, respectively.

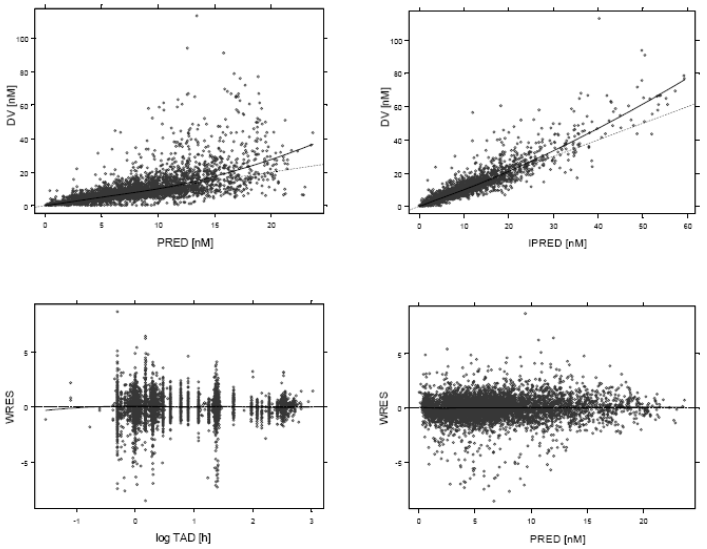


Figure 41: Basic goodness-of-fit plots for the final population PK model
Source: Report on Combined Population Pharmacokinetic Analysis for Linagliptin (pg 82)

Reviewer's Comment
The sponsor's conclusions based on assessment of impact of each single covariate on $AUC_{\tau,ss}$ is acceptable. However, the combined effect of all covariates was also evaluated and is described under section 3.

The goodness of fit plots indicates that the final model adequately describes the linagliptin pharmacokinetics.

Table 29: Parameter estimates from the final population PK model

Parameter	Value		Description
Fixed effects			
F1 [%]	100	FIX	Typical absolute bioavailability
F1 in study 1218.6 [%]	169		Typical absolute bioavailability in study 1218.6 relative to F1
WT_F1[1)]	-0.958		% change in F1 per kg change from the median weight of the population
KA [1/h]	0.933		Typical absorption constant formulation PiB
KA [1/h]	0.795		Typical absorption constant formulation TF2
KA [1/h]	0.441		Typical absorption constant formulation TF2b
DOSE_KA[2)]	-6.51		% change in KA per dose unit change from the 5 mg dose group
V2/F1 [L]	715		Typical central volume of distribution
Q3/F1 [L/h]	412	FIX	Typical inter-compartmental clearance between central compartment and peripheral compartment 1
V 3/F1 [L]	1650	FIX	Typical volume of distribution of the peripheral compartment 1
CL/F1 [L/h]	258		Typical clearance of the unbound concentration
GGT_CL[3)]	-0.0339		% change in CL/F1 per U/L change from the median GGT of the population
BMAX [nmol/L]	4.97		Typical concentration of binding sites in the central compartment (male)
DPP_BMAX[4)]	0.00332		% change in BMAX per RFU change from the median DPP of the population
DOSE_BMAX[4)]	3.41		% change in BMAX per dose unit change from the 5 mg dose group
AGE_BMAX[4)]	0. 561		% change in BMAX per year change from the median age of the population
SEX_BMAX[4)]	0.457		Absolute change in BMAX between males and females
KD [nmol/L]	0.0652	FIX	Typical affinity constant of the nonlinear binding
AMAX2/F1 [nmol]	1650	FIX	Typical amount of binding sites in the peripheral compartment 1
random effects			
IIV_F1 [CV%]	47.4		Inter individual variability in the absolute bioavailability
Cor_F1_CL	-0.765		Correlation between IIV_F1 and IIV_CL
IIV_CL [CV%]	27.5		Inter individual variability in the clearance of the unbound concentration
IIV_KA [CV%]	76.4		Inter individual variability in the absorption constant
IIV_V2 [CV%]	24.4		Inter individual variability in the central volume of distribution
IIV_BMAX [CV%]	15.0		Inter individual variability in the concentration of central binding sites
IOV_F1 [CV%]	40.0		Intra individual variability in the absolute bioavailability
prop. residual variability [%]	13.6		Residual variability Phase I
prop. residual variability [%]	38.3		Residual variability Phase IIb

Source: Report on Combined Population Pharmacokinetic Analysis for Linagliptin (pgs 79-81)

3 Reviewer's Analysis

3.1 Introduction

An independent analysis was performed to understand the non-linear behavior of linagliptin using population PK model, to assess the combined effect of covariates on $AUT_{\tau,ss}$, and to evaluate the exposure-response relationship for linagliptin.

3.2 Objectives

Analysis objectives are:

1. To perform sensitivity analysis on final model to evaluate linagliptin's non-linear PK behavior
2. To assess the combined effect of covariates on $AUT_{\tau,ss}$
3. To evaluate the exposure-response (ΔHbA1c) relationship for linagliptin by using the simulated $AUT_{\tau,ss}$

3.3 Methods

3.3.1 Data Sets

Data sets used are summarized in Table 30.

Table 30: Analysis Data Sets

Study Number	Name	Link to EDR
Exposure-response analysis 1218-005 and 1218-006	adeff.xpt datasets from both trials	\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets
Population PK analyses 1218-002, 1218-003, 1218-005 and 1218-006	pkdata1.xpt	\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218poppk\analysis
Cumulative safety by dose and by time (Figure 14)	aeads1.xpt aeads2.xpt aeads3.xpt aeads4.xpt	\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\pooled-datasets-orig-nda-1\analysis

3.3.2 Software

Simulations for exposure-response analysis were performed with NONMEM 6. Simulations for sensitivity analysis were performed with Berkley Madonna. S-plus software was used for data processing and for making the graphs.

3.3.3 Models

The final population PK model described above was used to perform all simulations. For sensitivity analysis different scenarios were simulated based on one or more of the following conditions: AMAX2=0 or BMAX=0 or Q3=0. This analysis was performed with Berkeley Madonna.

To assess the combined effect of all covariates, we incorporated each covariate in the model at their median values for a male patient. Next the individual covariates were changes to two extremes (5^{th} and 95^{th} percentiles of covariate distribution for continuous covariates). We compared the resulting $AUC_{\tau,ss}$ values with the median $AUC_{\tau,ss}$ values. This analysis was also performed with Berkeley Madonna.

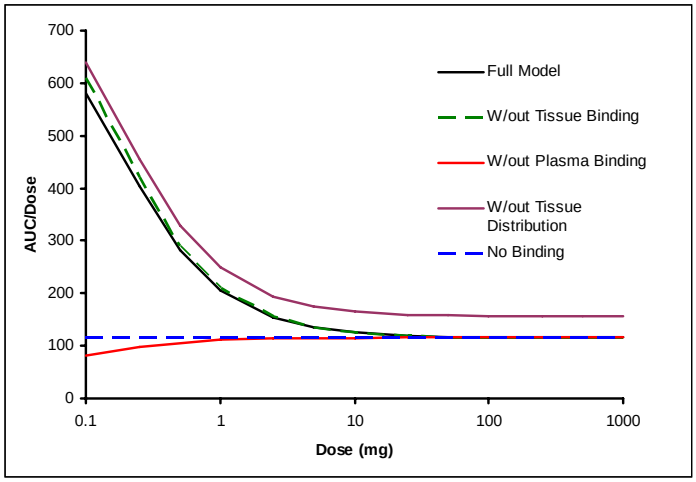
To evaluate the exposure response relationship, AUC_{ss} for a dosing duration was simulated for all patients on trials 1218.5 and 1218.6 in NONMEM. An additional differential equation was added to NONMEM code to calculate the AUC based on total concentration (C_{tot}) in central compartment (i.e., $d/dt(A_4)=C_{tot}$), where the parameter A_4 would represent the integral of the linagliptin concentration (i.e., AUC). This model was initialized at steady-state by defining SS=1 in data file. The simulated $AUC_{\tau,ss}$ from all patients on trials 1218.5 and 1218.6 were pooled together to calculate exposure quartiles, and corresponding change in HbA1c for each exposure quartile was also calculated. The relationship between the exposure quartiles and reduction in HbA1c was examined (see Figure 13 in section 2.2.6) and the range of simulated exposures for each dose was also depicted in the same figure for comparative purposes.

3.4 Results

Sensitivity analysis for evaluation of linagliptin's non-linear PK behavior

Some components of the model were removed to assess their impact on model based predictions of linagliptin PK. Removal of tissue binding (AMAX2=0) and tissue distribution (Q3=0) has minimal impact on linagliptin PK (Figure 42). Removal of plasma binding (BMAX=0) reduces the linagliptin concentrations to the level of no binding (BMAX=0 and AMAX2=0), suggesting that binding in the central compartment is the main determinant of linagliptin's non-linear PK behavior (Figure 42). This figure also shows that PK starts becoming linear at doses of about 5 mg and above under assumption that concentration dependent binding of linagliptin to proteins in central and peripheral compartment is the only variable affecting linagliptin PK.

A.



B.

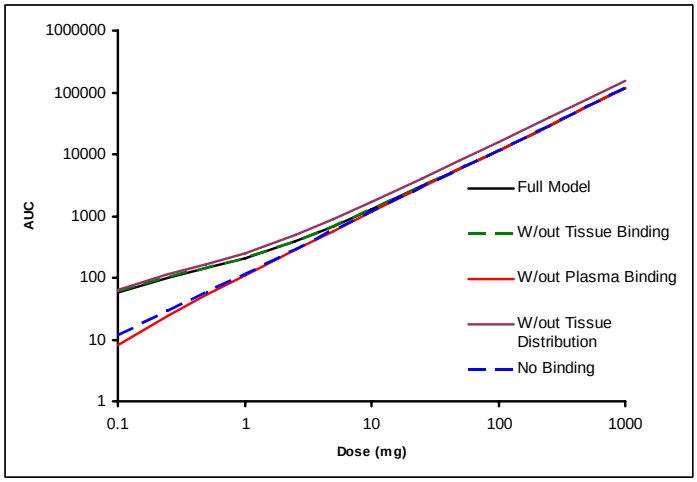


Figure 42: Sensitivity analysis on the final population PK model. Impact of modifications in model on (A) dose normalized AUC and (B) AUC.

Assessment of the combined effect of covariates on $AUT_{\tau,ss}$

In addition to the effect of individual covariates on $AUT_{\tau,ss}$ as reported in Table 28, we also compared the effect of combined covariates. No significant effect on $AUT_{\tau,ss}$ was observed when all statistically significant covariates were included in the model together (Table 31), similar to that observed for impact of single covariates.

Table 31: Investigation of impact of combined covariates on $AUC_{\tau,ss}$ after administration of 5 mg linagliptin

Model parameter	Statistically significant covariate	Categories	Typical $AUC_{\tau,ss}$ [nM*h]	%difference from median
F1	WT	P.05 (67 kg)	164	+6.5%
		Median (88 kg)	154	
		P.95 (117 kg)	141	-8.4%
BMAX	AGE	P.05 (42 years)	143	-7.1%
		Median (60 years)	154	
		P.95 (73 years)	163	+5.8%
	SEX	Male	154	
		Female	165	+7.1%
	DPP	P.05 (8025 RFU)	138	-10%
		Median (12497 RFU)	154	
		P.95 (18623 RFU)	177	+15%
CL	GGT	P.05 (9.4)	154	< -1%
		Median (33)	154	
		P.95 (158)	156	+1.3%

Exposure-response (ΔHbA1c) relationship for linagliptin

Please see section 2.2.6 for results from exposure-response analysis.

4 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviewes\PM Review Archive\2011\Linagliptin_NDA201280_LJ
popPKrun708.doc	Pop PK covariate assessment to verify labeling claims and Berkley Madonna code	\PPK Analyses\
Sim exposure_dataset_Lina_updated 112310.ssc	Exposure-response analysis	\ER Analyses\Exposure Response\
Dose response 102110.ssc	Dose-response analysis	\ER Analyses\Dose Response\
Adverse Event Rates Timecourses ISS Lina.ssc	Cumulative safety analysis by dose and by time	\ER Analyses\Cumulative safety by dose and time \
RenalImpairment.ssc	Comparison of trough concentrations across renal impairment groups	\PK Analyses\Renal Impairment\
Dose exposure.ssc	Exploratory analysis to evaluate linagliptin's non-linear PK behavior	\PK Analyses\Dose Exposure\

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

/s/

LOKESH JAIN
03/07/2011

JUSTIN C EARP
03/08/2011

CHRISTINE E GARNETT
03/08/2011

SALLY Y CHOE
03/09/2011

INDIVIDUAL STUDIES REVIEW

NDA: 201280	Submission Date: 07/02/2010
Brand Name	TBD
Generic Name	Linagliptin
Clinical Pharmacology & Pharmacometric (PM) Reviewer	Lokesh Jain, Ph.D.
Secondary PM Reviewer	Justin Earp, Ph.D.
PM Team Leader	Christine Garnett, Pharm.D.
Clinical Pharmacology Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products
Sponsor/Authorized Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Type; Code	Original NDA 505(b)(1); Standard
Formulation; Strength(s)	IR Tablet ; 5 mg
Indication	To improve glycemic control in patients with type 2 diabetes mellitus

ADME In-Vitro STUDIES

1 Absorption and Transporters

Study # C-10165-040-0404

Title: Investigation of the passive and active (P-glycoprotein mediated) transport of linagliptin in vitro by means of permeability measurements across confluent Caco-2 cell monolayers.

- **Objective:** To classify the in vitro permeability of the linagliptin and to assess whether linagliptin interacts with the drug efflux transporter P-glycoprotein (P-gp).
- **Method:** In vitro apical-to-basal (a-b) and basal-to-apical (b-a) permeability was assessed across monolayers of the human colon carcinoma derived cell line Caco-2, a well established in vitro model of the intestinal epithelium.
- **Results:** Linagliptin is transported in apical-direction and has concentration-dependent permeability coefficients in both transport directions. Following comparison with references of mannitol, atenolol, and propranolol, linagliptin was found to have moderate intrinsic passive permeability. At 10 µM and 20 µM drug concentration, the b-a permeability was 54.4 fold greater than the a-b permeability. At the highest concentration of 300 µM the b-a permeability was still 8.6 times higher than the a-b permeability, indicating that the transport was not saturated at this concentration. The vectorial transport investigated at 10 µM and 20 µM linagliptin was almost completely inhibited in the presence of 12 µM cyclosporin A and 200 µM verapamil indicating that linagliptin is a substrate for P-gp. The MRP Inhibitor MK571 (50 µM) had no effect on permeability.

  Linagliptin inhibited the P-gp-mediated a-b and b-a transport of the P-gp substrate digoxin across the Caco-2 monolayers in a concentration-dependent manner. The mean apparent IC_{50} value of approximately 55 µM, determined for the inhibition of the b-a transport of digoxin, indicated linagliptin as a weak inhibitor of P-gp transporter.
- **Conclusions:** Linagliptin has moderate permeability and is a substrate and a weak inhibitor of P-gp (IC_{50}=55µM)

Study # A056/08HH

Title: Impact of intestinal P-gp mediated efflux of linagliptin on its oral pharmacokinetics in the rat

- **Objective:** To investigate the influence of intestinal P-gp on oral bioavailability of linagliptin and the effect of intestinal P-gp inhibition by a high oral dose of linagliptin on its own oral pharmacokinetics
- **Method:** Single oral doses of 2.16 or 31.8 µmol/kg (1 or 15 mg/kg) linagliptin were administered to male Wistar rats pre-treated with either 5 µmol/kg Zosuquidar p.o. (resulting in effective and selective inhibition of intestinal P-glycoprotein) or vehicle (5% glucose solution) p.o.. The plasma concentration – time profiles of linagliptin and CD1750 XX were determined for over 72 hrs.

- **Results:** Oral absorption of linagliptin is enhanced by inhibition of intestinal P-gp, resulting in an over-proportional increase in C_{max} and AUC_{0-72h} (Table 1). The extent of the Zosuquidar-effect was dependent on the oral dose of linagliptin; C_{max} was elevated by a factor of approximately 14 and 1.4 and AUC_{0-72h} increased by a factor of 2.1 and 1.4 fold for doses of 2.16 and 31.8 µmol/kg, respectively.

Table 1: Summary of changes in C_{max} and AUC following inhibition of P-gp by Zosuquidar

		Group 1	Group 2	Group 3	Group 4
Dose BI 1356 BS	[µmol/kg]	2.12	2.12	31.8	31.8
	[mg/kg]	1	1	15	15
Pre-treatment Zosuquidar		-	+	-	+
C(max)/dose	[nmol/L]/[µmol/kg]	12.0	164	88.7	120
AUC(0-72h)/dose	[nmol·h/L]/[µmol/kg]	147	309	227	309
C(max) 1750/1356*	[%]	3.5	2.6	4.1	4.5
AUC(0-72h) 1750/1356°	[%]	0.6	2.0	4.6	5.8

* Ratio C(max) CD 1750 XX / C(max) BI 1356 BS

° Ratio AUC(0-72h) CD 1750 XX / AUC(0-72h) BI 1356 BS

- **Conclusion:** Oral absorption of linagliptin is enhanced by inhibition of intestinal P-gp.

Study # a095-08fu-a558-08bc

Title: Effect of P-gp inhibition on biliary excretion of linagliptin in rats

- **Objective:** To investigate the effect of P-gp inhibition on biliary excretion of total radioactivity after i.v. administration of [^{14}C] linagliptin to rats
- **Method:** One group of rats was treated with the P-gp inhibitor Zosuquidar administered by intravenous infusion with a constant rate of 7.5 mg/kg/h and another group of rats received vehicle (saline) infusion. Both groups of rats received a single intravenous bolus administration of 15 mg/kg (= 31.7 µmol/kg) [^{14}C] linagliptin and bile was sampled in 30 min intervals up to 6 h after dosing of [^{14}C] linagliptin.
- **Results:** The biliary excretion of parent drug within 6 hours was significantly reduced by P-gp inhibition (from 8.2% to 3.2% of dose), whereas the respective biliary excretion of its metabolites (total radioactivity –linagliptin) within 6 hours was unaffected (29.8% versus 30.8% of dose).
- **Conclusions:** P-gp inhibition reduces biliary elimination of linagliptin.

Study # PK05023

Title: Investigation of human transporters involved in the influx and efflux of linagliptin

- **Objective:** To investigate whether linagliptin is a substrate and/or an inhibitor of SLC and ABC transporters.
- **Method:**
  - Uptake of [^{14}C] linagliptin in HEK293 cells expressing OATP2, OATP8, OATP-B, OCT1, OCT2, OCTN1, OCTN2, OAT1, OAT3 or OAT4 was compared with that in the respective vector-transfected HEK293 cells.
  - The potential of linagliptin to inhibit SLC transporters was investigated by measuring the uptake of a suitable radiolabelled probe substrate in the absence or presence of linagliptin in the concentration range of 1 µM to 100 µM.

- To investigate whether linagliptin is a substrate for human ABC transporters, basal-to-apical (B to A) transport and apical-to-basal (A to B) transport of [^{14}C] linagliptin in P-gp (or MDR1)-expressing LLC-PK1 cells, MRP2-expressing MDCKII cells and BCRP-expressing MDCKII cells were compared with those in the respective parental cells.
- To determine the potential of linagliptin to inhibit P-gp, MRP2 and BCRP activities, bi-directional transport and intravesicular transport studies were performed in the absence or presence of linagliptin at concentrations up to 100 µM.

- **Results:**
  - Significant uptake of linagliptin was observed in OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2-expressing cells, suggesting the possible occurrence of OATP8-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and reabsorption of linagliptin in vivo. No significant uptake of linagliptin was mediated by OATP2, OATP-B, OCT1, OAT1 and OAT3.
  - There was no significant inhibition of OATP-B, OCT2, OAT1, OAT3, OAT4 and OCTN2 activities by linagliptin. OATP2, OATP8 and OCTN1 activities were slightly inhibited (<34%) by linagliptin at the highest concentration of 100 µM. OCT1 and OATP2 activities were significantly inhibited with IC_{50} values of 45.2 µM and 69.7 µM, respectively.
  - Efflux ratios for P-gp, MRP2, and BCRP transporters were 35.1, 0.640 and 0.469, respectively, indicating that linagliptin is a substrate of P-gp but is not a substrate of MRP2 or BCRP.
  - Linagliptin inhibited P-gp transporter (vectorial transport of digoxin) with IC_{50} value of 66.1 µM. Linagliptin did not inhibit MRP2 and BCRP.
- **Conclusions:** Linagliptin is a substrate and an inhibitor of P-gp and some SLC transporters. However, given the micromolar concentrations of linagliptin that are needed for inhibition of P-gp and the relatively low doses of linagliptin that are anticipated for therapy, in vivo inhibition of P-gp is considered as relatively unlikely.

2 Distribution

Study # A016_04FU

Title: linagliptin: Species comparison of in vitro plasma protein binding and distribution between blood cells and plasma.

- **Objective:** To investigate the extent of binding of [^{14}C]-radiolabelled linagliptin to human, minipig, dog and rat plasma proteins *in vitro*.
- **Method:** Plasma from human, minipig, dog and rat were used to determine the extent of protein binding by equilibrium dialysis using concentrations of about 30, 300 and 3000 nM [^{14}C] linagliptin. In addition, the distribution of drug-related radioactivity between blood cells and plasma was investigated *in vitro* at a concentration of about 300 nM [^{14}C] linagliptin. The radioactivity was quantified by means of liquid scintillation counting.
- **Results:** A significant species difference in protein binding was observed with a low extent of plasma protein binding in minipigs and a moderate extent of binding to plasma proteins in

humans, dogs and rats *in vitro*. Binding sites saturated at higher plasma concentrations of [^{14}C] linagliptin (see protein binding data in human in Table 2). In human and dog blood, [^{14}C] linagliptin is distributed predominantly into plasma, whereas in rat blood, [^{14}C] linagliptin related radioactivity is almost equally distributed between blood cells and plasma *in vitro*.

Table 2: Mean binding of [^{14}C] linagliptin to human plasma proteins with respect to gender and concentration of [^{14}C] linagliptin. f_b shows the bound fraction of radioactivity in %.

gender	[^{14}C]BI 1356 BS concentration intended [nM]	achieved mean [nM]	SD [nM]	f_B mean (%)	SD (%)
male		5170	36.3	82.8	0.3
female		5320	81.2	85.9	0.6
male & female	**3000**	**5230**	**92.0**	**84.0**	**1.7**
male		3030	21.8	84.6	0.4
female		2920	234	84.3	1.9
male & female	**3000**	**2980**	**161**	**84.9**	**1.3**
male		416	4.36	85.0	0.9
female		417	8.23	88.3	0.3
male & female	**300**	**417**	**5.90**	**86.6**	**1.9**
male		209	4.14	86.0	0.8
female		208	0.415	87.5	0.1
male & female	**300**	**208**	**2.70**	**86.7**	**1.0**
male		30.9	0.334	88.6	0.9
female		30.5	0.497	90.0	0.7
male & female	**30**	**30.7**	**0.441**	**89.3**	**1.0**

- **Conclusions:** linagliptin shows concentration dependent plasma protein binding in the concentration range of 30 to 3000 nM.

Study # A083_07FU

Title: Investigation on the concentration dependency of the in vitro plasma protein binding of [3H] linagliptin in humans, wildtype and DPP-4 knockout mice and wildtype and DPP-4 deficient rats.

- **Objective:** To investigate the concentration dependency in more detail at lower linagliptin concentrations in mouse, rat and human plasma. Also to evaluate the binding in plasma from DPP-4 deficient ("knockout") mice and DPP-4 deficient Fischer rats
- **Method:** Plasma protein binding of linagliptin was determined by equilibrium dialysis using [3H]-labeled linagliptin
- **Results:**
  - The concentration dependent binding of linagliptin to DPP-4 was observed in wild-type mouse, wild-type rat and human plasma but was absent in DPP-4 knockout mice and DPP-4 deficient rats (Figure 1). Thus, the concentration dependency was shown to originate

from saturation of the binding of linagliptin to soluble DPP-4 in plasma. The maximum fraction bound of linagliptin is around 99% in mouse, rat and human plasma. Saturation of linagliptin binding to plasma DPP-4 occurs at plasma concentrations exceeding 1 nM linagliptin, leading to a steep decrease of the fraction bound and hence a prominent increase of the unbound fraction between 1 and 100 nM linagliptin. At plasma concentrations beyond 100 nM, the plasma protein binding is constant over a broad concentration range with a bound fraction between 70 and 80% (Table 3).

- The binding of linagliptin to DPP-4 is of very high affinity with an affinity constant of about 2-3 x 10^{10} M^{-1} in wildtype mouse, rat and human plasma. By fitting the sigmoidal curve for f_B vs. concentrations, indications on a positive cooperative effect in the binding of linagliptin to both binding sites of a DPP-4 dimer were found.
- Low binding of linagliptin to human albumin (f_B = 48.2%) and human alpha-1 acid glycoprotein (f_B = 32.8%) was observed in vitro using isolated purified proteins.

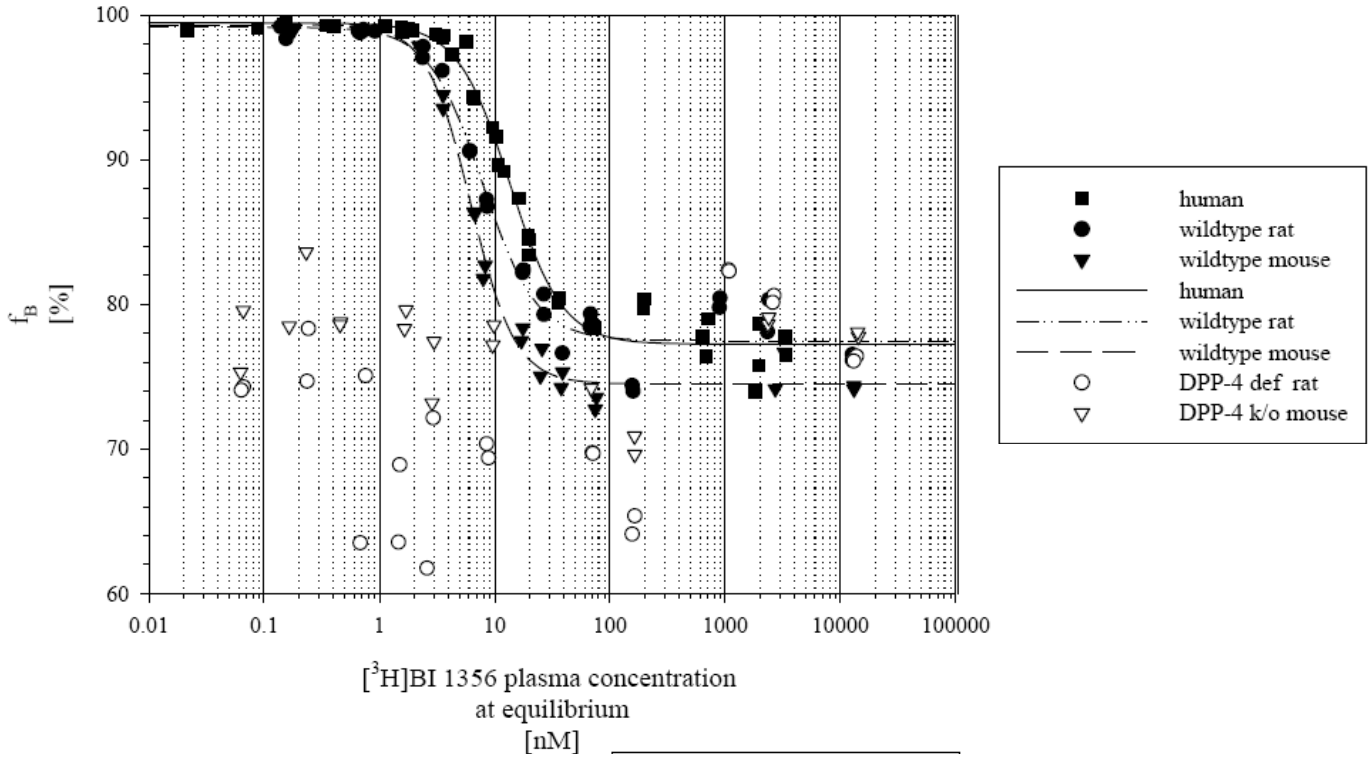


Figure 1: Concentration dependency of the plasma protein binding of [3H] linagliptin in mouse (wildtype and DPP-IV knockout), rat (wildtype and DPP-IV deficient) and human plasma including the plots of the nonlinear regressions (wildtype animals and human only).

Table 3: Plasma protein binding data of [^{3}H] linagliptin in humans. All concentrations refer to the values determined at equilibrium

target concentration [nM]	plasma conc. (achieved plasma conc.) [nM]	free conc. (achieved acceptor conc.) [nM]	bound conc. (plasma conc. – buffer conc.) [nM]	bound/free	f_B (%)
60000	29900	10500#	19300#	2.83	64.7
60000	29900	9370#	20500#	3.19	68.6
20000	10900	3060#	7840#	3.57	72.0
20000	11200	3120#	8110#	3.60	72.2
10000	5860	1450	4410	4.05	75.3
10000	5840	1440	4400	4.06	75.4
6000	3340	785	2550	4.25	76.5
6000	3310	736	2580	4.50	77.8
3000	1960	474	1480	4.13	75.8
3000	1970	421	1550	4.68	78.6
3000	1840	480	1360	3.84	73.9
3000	1810	472	1340	3.84	74.0
1000	641	143	498	4.47	77.6
1000	640	142	498	4.50	77.8
1000	683	161	522	4.24	76.4
1000	714	150	564	4.77	79.0
300	197	39.9	157	4.93	79.7
300	197	38.6	158	5.10	80.4
200	141	39.2	101	3.59	72.1
200	142	41.3	101	3.44	71.0
100	70.0	15.0	54.9	4.65	78.5
100	69.2	14.8	54.4	4.67	78.6
80	71.7	15.4	56.3	4.66	78.5
80	73.6	15.9	57.6	4.62	78.4
40	36.8	7.19	29.6	5.11	80.4
40	35.7	7.10	28.6	5.03	80.1
30	19.7	3.27	16.5	6.03	83.4
30	20.0	3.10	16.9	6.46	84.5
20	19.4	3.01	16.4	6.47	84.5
20	19.6	2.99	16.6	6.55	84.7
15	16.4	2.07	14.3	7.90	87.3
15	12.3	2.44	9.90	5.05	80.2
11	12.0	1.30	10.7	9.24	89.2
11	10.7	1.11	9.57	9.66	89.6
10	6.67	0.384	6.29	17.3	94.2
10	6.55	0.372	6.18	17.6	94.3
8	10.2	0.858	9.38	11.9	91.6
8	9.56	0.74	8.82	12.9	92.3
6	4.26	0.116	4.15	36.8	97.3
6	5.62	0.102	5.52	55.0	98.2
6	3.55	0.0551	3.50	64.5	98.4
6	3.62	0.0514	3.57	70.4	98.6
4.5	3.10	0.0399	3.06	77.7	98.7
4.5	3.32	0.0463	3.27	71.8	98.6
3.5	1.79	0.0168	1.77	106	99.1
3.5	1.94	0.02	1.92	96.8	99.0
3	1.56	0.0129	1.55	121	99.2
3	1.57	0.0178	1.56	88.4	98.9
1.5	1.12	0.00829	1.11	135	99.3
1.5	1.14	0.00846	1.13	135	99.3
1	0.404	0.00311	0.401	130	99.2
1	0.396	0.00309	0.393	128	99.2
§1	0.809	0.0501	0.759	16.2	93.8
§1	0.818	0.00694	0.811	118	99.2
§1	0.759	0.00767	0.752	98.9	99.0
§1	0.765	0.00965	0.756	79.3	98.7
§1	0.66	0.00603	0.654	109	99.1
§1	0.672	0.00656	0.665	102	99.0
§1	0.615	0.00611	0.609	101	99.0
§1	0.614	0.00544	0.609	113	99.1
0.4	0.347	0.00238	0.345	146	99.3
0.4	0.346	0.00245	0.343	141	99.3
0.3	0.0881	0.00078	0.0873	113	99.1
0.3	0.082*	0.00249*	0.0795*	32.9*	97.0*

Table 3: Continued

target concentration [nM]	plasma conc. (achieved plasma conc.) [nM]	free conc. (achieved acceptor conc.) [nM]	bound conc. (plasma conc. – buffer conc.) [nM]	bound/free	f_B (%)
§0.3	0.262	0.00233	0.26	113	99.1
§0.3	0.265	0.00363	0.262	73.0	98.6
§0.3	0.217	0.00223	0.214	97.2	99.0
§0.3	0.221	0.00227	0.219	97.7	99.0
§0.3	0.227	0.00218	0.225	104	99.0
§0.3	0.226	0.00213	0.224	106	99.1
§0.3	0.204	0.00154	0.203	133	99.2
§0.3	0.20	0.00161	0.198	124	99.2
0.1	0.0217	0.000224	0.0214	96.5	99.0
0.1	0.0217	0.000229	0.0214	94.8	98.9
***0.03*	*0.00498*	*0.0000979*	*0.00488*	*50.8*	*98.0*
***0.03*	*0.00521*	*0.0000932*	*0.00511*	*55.8*	*98.2*
0.02	0.155	0.000906	0.154	171	99.4
0.02	0.149	0.00100	0.148	148	99.3
***0.01*	*0.0019*	*0.00005*	*0.00185*	*41.0*	*97.6*
***0.01*	*0.00171*	*0.00018*	*0.00153*	*9.37*	*89.3*

§ data generated in plasma of individuals
# not included into bound vs. free regression (conc. >5000 nM)
* excluded (outlier)
** <25 dpm/aliquot buffer, excluded

- **Conclusion:** Linagliptin shows concentration dependent (saturable) binding to DPP-4.

Study # A033/05FU

Title: [^{14}C] linagliptin: Species comparison of *in vitro* protein binding in mouse, rabbit and cynomolgus monkey plasma

- **Objective:**
  To determine the extent of plasma protein binding for mice, rabbit, cynomolgus monkey, and humans in vitro.
- **Method:**
  The protein binding was determined by equilibrium dialysis using concentrations of 30, 300 and 3000 nmol/L [14C] linagliptin
- **Results:**
  In human plasma, the maximum protein binding was high (approx. 97 %) at concentration of 3 nmol/L and lower. At concentrations of 30 nmol/L binding reduced to 89% (Table 4).

Table 4: Mean binding of [14C] linagliptin to plasma proteins in various species given as bound fractions (f_B, means of males and females combined)

species	target concentration of [^{14}C]BI 1356 BS [nmol/L]	mean f_B %
CD1-Mouse	30	78.2
	300	74.7
	3000	72.7
rabbit (only females)	30	84.3
	300	81.5
	3000	79.6
cynomolgus monkey	30	82.0
	300	72.2
	3000	70.4
human	1	96.3
	3	97.9
	30	88.5

- **Conclusion:**

Linagliptin shows concentration dependent binding to plasma proteins

---

Study # A099/08FU

Title: Concentration dependency of the distribution of [^{14}C] linagliptin between blood cells and plasma in man.

- **Objective:** To investigate whether the concentration dependent change in the bound fraction in plasma has also consequences for its distribution between blood cells and plasma.
- **Method:** The distribution in blood was investigated using fresh human blood spiked with [^{14}C] linagliptin and subsequent evaluation of radioactivity concentrations in plasma and whole blood by two separate methods (Table 5).
- **Results:** The distribution of linagliptin in blood cells was found to be concentration dependent (Table 5). At very low concentrations, linagliptin is almost completely distributed into the plasma space, whereas at higher concentrations an additional distribution into or onto blood cells occurs. The concentration dependency is most likely due to changes in plasma protein binding because of saturable binding to DPP-4.

Table 5: Geometric mean concentration ratio of radioactivity in blood cells and plasma of linagliptin in human blood

Target conc. blood:		1 nM	5 nM	10 nM	50 nM	100 nM	500 nM	1000 nM
standard method	**gmean**	0.136	0.144	0.256	0.415	0.429	0.484	0.490
	gSD	2.144	1.516	1.169	1.086	1.051	1.025	1.041
	gCV (%)	88.8	43.4	15.7	8.3	4.9	2.5	4.0
silicon oil method	**gmean**	0.119	0.192	0.295	0.465	0.459	0.532	0.522
	gSD	1.441	1.126	1.066	1.062	1.058	1.066	1.047
	gCV (%)	37.8	12.0	6.4	6.0	5.7	6.4	4.6

- **Conclusion:** At low concentrations, distribution of linagliptin into red blood cells is minimal

3 In vitro Metabolism

Study # A168_04LU

Title: Investigation of the in vitro metabolism of [^{14}C] linagliptin

- **Objective:** To investigate the contribution of human cytochrome P450 enzymes involved in the in vitro metabolism of [^{14}C] linagliptin.
- **Method:** Human and rat liver microsomes, human and rat liver homogenate, human kidney microsomes and human hepatocytes were used for experiments. Additionally, the involvement of monoamine oxidases (MAOs) was investigated by use of expressed MAOs and human liver mitochondria. Formation of [^{14}C] linagliptin metabolism products was investigated using radiolabeled [^{14}C] linagliptin and HPLC with radioactivity detection.
- **Results:**
  - In vitro metabolism of [^{14}C] linagliptin by human liver microsomes was low and often close to background radioactivity. Only two metabolites U3 and U7 were formed consistently in quantifiable amounts. In metabolite U7, the amino function of the piperinidyl moiety was substituted by a hydroxy group (later denominated as CD1790). Metabolite U3 involved oxidation in quinazoline moiety.
  - Incubations with human hepatocytes also resulted into very low overall substrate turnover and only minor proportions of metabolites U3 and U7 were formed.
  - Metabolite formation was not observed in incubations containing mitochondria or expressed MAOs. No turnover of [^{14}C] linagliptin by human kidney microsomes was observed.
  - Experiments using recombinant CYPs and inhibition experiments with enzyme specific chemical inhibitors suggested that linagliptin is metabolized by CYP3A4 and no other CYP enzymes were involved.
  - Ketoconazole inhibited the formation of metabolites U3 and U7, confirming that these metabolites were formed by CYP3A4.
  - Linagliptin was a competitive inhibitor of MAO-B with a Ki of 2.39 µM.
- **Conclusion:** Extent of metabolism for linagliptin is low and only CYP3A4 enzyme is involved in metabolism.

4 In vitro Metabolite Identification

Study # A439_05BC

Title: Metabolism of linagliptin in human

- **Objective:** To investigate the metabolism of linagliptin in samples of clinical trial no. 1218.1.
- **Method:** The search of linagliptin-metabolites in plasma and urine samples was performed by ESI-QTOF mass spectrometry using a modified high resolution parent ion discovery

experiment. The elucidation of metabolite structures was accomplished by the detailed analysis of high resolution product ion spectra of the identified metabolite [M+H]+-ions.

- **Results:** Linagliptin was the dominant species in plasma and urine. In samples after administration of linagliptin dose of 25 mg/subject, M474(1) or CD1790 (substitution of amino function of piperinidyl moiety by hydroxy group, Figure 2) were identified with high relative abundance in plasma. In urine the following metabolites were identified with low abundance: M489(1), M490(1), M506(1) and M476(1). Other metabolites were found in trace amounts.

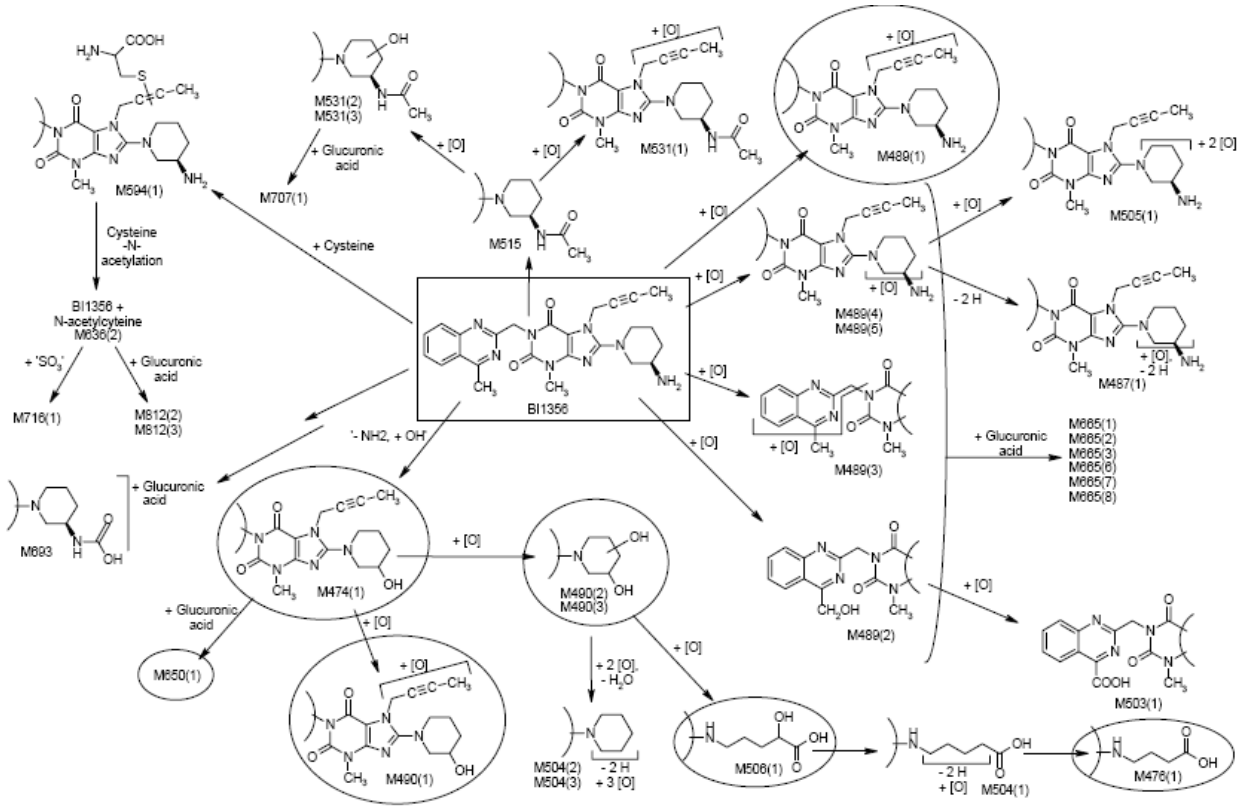


Figure 2: Metabolic fate of linagliptin (not 14C-labelled) in healthy male volunteers: The parent compound (rectangle) was the dominant species in urine and plasma after administration of the anticipated maximum therapeutic oral dose of 25 mg linagliptin; metabolites in plasma are indicated by a circle

- **Conclusion:** Overall, metabolism is of subordinate importance for the elimination of linagliptin in humans.

Study # A495_06BC

Title: Metabolism of linagliptin in healthy male volunteers

- **Objective:** To investigate the metabolite pattern of linagliptin in healthy male volunteers who was administered [14C] linagliptin intravenously and orally at a dose of 5 mg (10.6 µmol) and 10 mg (21.2 µmol), respectively.
- **Method:** Subsequent to dosing, samples of plasma, urine and feces were obtained and quantitatively analyzed for the presence of drug related compounds. The metabolite pattern was assessed by HPLC coupled to radioactivity detection.
- **Results:**
  Plasma: Metabolite pattern of linagliptin in plasma after intravenous and oral administration is shown in Table 6 and Table 7, respectively. Majority of drug in plasma remains in form of parent compound both after oral and intravenous administration. M474(1) with the amino group of the piperidine moiety substituted by a hydroxyl group (also referred as CD 1790) was identified as a major metabolite with 16.9% of sample radioactivity in pooled samples after oral administration. In addition, the metabolites M665(8), formed by oxidation followed by glucuronidation of the parent compound and M650(1), formed by glucuronidation of M474(1) accounted together for 5.5% of sample radioactivity (Table 7).
  Feces and urine: Most of the elimination also occurs in form of parent compound (Table 8 and Table 9). Approximately 61% of the recovered drug after intravenous administration and 78% after oral administration were in form of parent compound. Metabolite M489(1), formed by oxidation of the methyl group of the butinyl side chain, was the predominant metabolite recovered in feces and urine.

Table 6: Metabolite pattern in plasma after a single intravenous dose of 5 mg (10.6 µmol) [^{14}C] linagliptin (arithmetic means of 6 individuals)

metabolite	1.5 h		3 + 6 h (sample pool)	
	[nmol/L]	(% of sample radioactivity)	[nmol/L]	(% of sample radioactivity)
BI 1356	104.1	93.5	28.3	83.9
M474(1)	6.2	5.6	3.7	10.9
M489(1)			0.2	0.7
M665(3)			0.4	1.2
M665(8) + M650(1)	1.0	0.9	0.9	2.7
m4			0.2	0.6
total	111.3	100.0	33.7	100.0

Table 7: Metabolite pattern in plasma after a single oral dose of 10 mg (21.2 µmol) [^{14}C] linagliptin (arithmetic means of 6 individuals)

metabolite	1.5 + 3 + 6 h (sample pool)	
	[nmol/L]	(% of sample radioactivity)
BI 1356	**17.3**	**74.2**
M474(1)	3.9	16.9
m4	0.7	3.1
M489(1)	0.1	0.3
M665(8) + M650(1)	1.3	5.5
total	23.3	100.0

Table 8: Metabolite pattern in urine and feces after a single intravenous dose of 5 mg (10.6 µmol) [^{14}C] linagliptin (arithmetic means of 6 individuals (% of dose administered))

metabolite	urine 0 - 48 h	faeces 0 - 240 h	urine + faeces total
BI 1356	**25.3**	**35.8**	**61.1**
M474(1)	0.1	2.5	2.6
M476(1) + M515(1)	0.1		0.1
M489(1)	0.3	9.3	9.6
M503(1)	0.2	1.2	1.4
M506(1)		4.0	4.0
M620(1)	< 0.1		< 0.1
M636(2)	0.1		0.1
M636(3,4)	0.2		0.2
M665(3)	0.4		0.4
M665(8) + M531(1,2)	0.7		0.7
m1	< 0.1		< 0.1
m2	0.1		0.1
m3	< 0.1	0.3	0.4
m5	< 0.1		< 0.1
total	27.5	53.2	80.7

Table 9: Metabolite pattern in urine and feces after a single oral dose of 10 mg (21.2 µmol) [14C] linagliptin (arithmetic means of 6 individuals (% of dose administered))

metabolite	urine 0 - 48 h	faeces 0 - 120 h	urine + faeces total
BI 1356	**3.9**	**74.1**	**78.0**
M474(1)	0.2	0.3	0.5
M489(1)	0.2	4.5	4.7
M503(1)	< 0.1	0.1	0.1
M504(2)	0.1		0.1
M515(1)	0.1		0.1
M531(2) + M490(1) + M506(1)		2.5	2.5
M650(1)	0.3		0.3
M665(3)	0.1		0.1
M665(8) + M490(1)	0.3		0.3
m1	0.1		0.1
m2	0.2		0.2
m3	< 0.1		< 0.1
m5	< 0.1		< 0.1
m6	< 0.1		< 0.1
total	5.5	81.5	87.0

- **Conclusions:** Linagliptin primarily remains in form of parent compound in plasma and most of it is also eliminated as parent compound.

5 Enzyme Inhibition

Study # A161_04LU

Title: Linagliptin: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions

- **Objective:** To investigate the inhibition of cytochrome P450-catalysed test reactions by linagliptin in liver microsomes of humans.
- **Method:** The test substrates were incubated with human liver microsomes in the presence of reduced form of β-nicotinamide adenine dinucleotide phosphate (NADPH) and the formation of the respective metabolites was quantified using sensitive and selective analytical techniques. Experiments were performed to test the inhibition of enzymes CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4.
- **Results:**
  - Linagliptin inhibited CYP 3A4 dependent testosterone 6β-hydroxylation with an IC_{50} of 36.3 µM and a Ki of 115 µM and CYP 3A4 dependent erythromycin N-demethylation with an IC50 of 41.6 µM. IC_{50} values for midazolam 1-hydroxylation and nifedipine oxidation were >100 µM. Inhibition of testosterone 6β-hydroxylation and erythromycin N-demethylation was mechanism-based with K_I/k_{inact} ratio of 43.2 and 222 µM, respectively, but the inhibition of nifedipine oxidation was not predominantly mechanism-based.
  - There was no inhibition of any of the other CYP isoenzymes that were investigated by this study.
- **Conclusion:**

Linagliptin was considered to be a moderate to poor mechanism based inhibitor of CYP 3A4

Study #A239_08LU

Title: CD 1790 XX: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions

- **Objective:** To investigate the inhibition of cytochrome P450-catalysed test reactions by CD 1790 XX in liver microsomes of humans.
- **Method:** The extent of inhibition of CD 1790 XX was assessed at concentrations of 0.1, 1, 10 and 100 µM for following enzymes: CYP 1A1, CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 4A11.
- **Results:**
  - CD 1790 XX was found to be a competitive inhibitor of CYP 2C9 and a mechanism-based inhibitor of CYP 3A4 with K_i values in the range of 8.28 to 25.2 µM.
  - CD 1790 XX was found to be a moderate mechanism-based inhibitor of CYP 3A4 with K_I and k_{inact} values of 88.3 µM and 0.25 min^{-1}.
  - Since the plasma concentration of CD1790 XX are in nM range ($C_{max,ss}$ of 12.6 nM for 10 mg dose in Trial 1218.23), it is unlikely that inhibition of CYP isozymes by CD 1790 would occur.
- **Conclusions:** CD 1790 XX is an inhibitor of CYP 2C9, CYP 2C19, and CYP 3A4. However, clinical drug-drug interactions based on inhibition of these enzymes by CD 1790 are unlikely.

6 Enzyme Induction

Study # 300866881 (**Document #** U08-1198-02)

Title: Evaluation of induction potential of cytochrome P450 isoforms by linagliptin in cultured human hepatocytes

- **Objective:** To determine the induction potential of cytochrome P450 (CYP) isoforms by linagliptin, in fresh cultured human hepatocytes.
- **Method:** linagliptin was incubated with hepatocytes from three donors at concentrations of 0.001, 0.005, 0.02, 0.2 and 2 µM. Induction was measured by *in situ* catalytic activity assays selective for CYP1A2, CYP2B6 and CYP3A4.
- **Results:**
  - At the tested concentrations linagliptin caused no induction of CYP 1A2, CYP 2B6 and CYP 3A4.
  - At the concentration of 2 µM after a 3-day treatment linagliptin caused a moderate reduction (16-30%) in CYP 1A2 activity in three donors, and a moderate reduction (30%-36%) in CYP 2B6 activity in two of the three donors.
  - The 2 µM concentration of linagliptin reduced CYP 3A4 activity by 48%, 68%, and 47% in three donors.
- **Conclusions:** Linagliptin is not an inducer of CYP1A2, CYP2B6 and CYP3A4. However, it is an inhibitor of CYP3A4.

PHARMACOKINETICS

1 Mass Balance Study

Study # 1218.7 (Document # U08-1363-01)

Title: Investigation of the metabolism and pharmacokinetics of 10 mg [^{14}C] linagliptin administered orally compared to 5 mg [^{14}C] linagliptin administered intravenously in healthy male volunteers in an open label, single-dose and parallel study design

- **Objective:** To determine the basic pharmacokinetics of linagliptin, its metabolite CD 1750, and radioactivity including excretion mass balance, excretion pathways and metabolism following the intravenous and oral administration of [^{14}C] linagliptin
- **Study design:** Parallel group, single dose, open-label study in healthy male volunteers.
- **Test drug and sample size:** 10 mg [^{14}C] linagliptin as oral (p.o.) solution and 5 mg [^{14}C] linagliptin as intravenous (i.v.) infusion over 1.5 hours. N=6 for both groups.
- **Results:**
  The overall recovery of the administered radio-labeled dose (about 90%) was considered essentially complete. Most of the radioactivity was excreted within 96 hours after oral and 120 hours after intravenous administration. See Tables 6 to 9 under study # A495_06BC for details of metabolite pattern in plasma, feces, and urine.
  Absorption: Absorption of [^{14}C] linagliptin was rapid; maximum concentrations were reached between 0.5 and 4 hours after dosing. Absorption was variable, showing double peak absorption profiles within the first 6 hours after oral administration. Linagliptin accounted for most of the observed plasma radioactivity. The fraction absorbed based on total radioactivity in plasma was 36.7%.
  Metabolism: see study # A495_06BC for details of metabolite pattern

Elimination: After both oral and intravenous administration, the majority of linagliptin (~90%) was excreted unchanged in the urine and feces. After oral administration, the dominant excretion pathway was the feces; only about 5.4% of total radioactivity was excreted in the urine. However, after intravenous infusion, about 31% of total radioactivity was excreted in the urine, likely because of increased unbound concentrations (see Tables 6 to 9 under study # A495_06BC).

2 Single Rising Dose (Oral)

Trial # 1218.1

Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of linagliptin as a solution at dose levels 2.5 to 5 mg and tablets at dose levels 25 to 600 mg administered to healthy male subjects in a randomized, double-blind, placebo-controlled trial, including an intra-subject bioavailability comparison of 100 mg linagliptin as tablet and as solution.

- **Objective:** To investigate safety, tolerability, pharmacokinetics and pharmacodynamics of linagliptin in dose range from 5 mg to 1200 mg
- **Study design:** placebo-controlled, randomized study blinded within each dose level. At each dose level 8 subjects were to be enrolled.
- **Test drug and sample size:** Linagliptin in tablet and solution dosage forms, taken orally in fasted state with 240 mL water. Sample size for each group is listed in Table 10.
- **Results:**
  The plasma concentration-time profiles for tested dose levels are shown in Figure 3 and PK parameters are summarized in Table 10. Linagliptin followed at least biexponential disposition kinetics. For doses 25 mg and above, two absorption peaks were observed in most subjects. The decline in plasma concentrations was steeper for the higher doses compared to that for lower doses, indicating nonlinear distribution and/or elimination processes.

  The values of $AUC_{0-\infty}$ increased in a less than proportional manner for doses between 2.5 mg and 10 mg, more than proportional manner for doses between 25 to 100 mg, and an almost statistically proportional behavior was observed for doses between 100 mg and 600 mg (Figure 4). Half-life, apparent clearance, and apparent volume of distribution were dose-dependent suggesting non-linearity. Fractional renal excretion was also dose dependent, and increased from being not measurable for the 2.5 mg dose (i.e., ~0%) to 32.7% for the 600 mg dose.

  Comparison of concentration-time profiles of linagliptin tablet versus solution
  The intra-individual comparison of 100 mg linagliptin given as a tablet or in solution form showed that plasma concentrations were considerably lower after administration of the solution compared to the tablet (Figure 6). This finding was contrary to the expectations and the reason for this behavior was unknown.

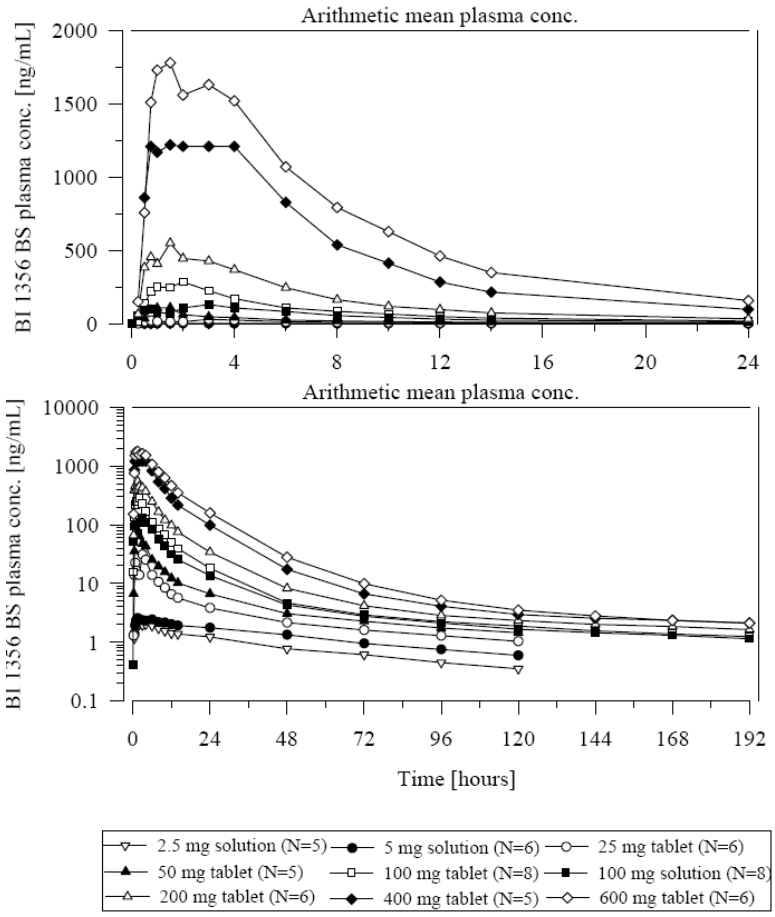


Figure 3: Arithmetic mean drug plasma concentration-time profiles of linagliptin (BI 1356) after single oral administration of 2.5 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 600 mg

Table 10: Key pharmacokinetic parameters of linagliptin after single oral administration of 2.5 to 600 mg dose

Dose (mg)	N	T_{max} (hr) Median (range)	gMean (gCV%)*					
			C_{max} (nM)	$AUC_{0-\infty}$ (nM.hr)	$t_{1/2}$ (h)	CL/F (mL/min)	V/F (L)	fe_{0-tz} † (%)
2.5 PIB£	5	2.1 (1.5-3.1)	4.4 (19)	290 (34)	79.9 (35)	303 (34)	2100 (13)	NC
5 PIB	6	1.5 (1.0-6.0)	5.7 (19)	427 (33)	69.7 (17)	413 (33)	2490 (27)	0.96 (70)
25 tab€	6	3.0 (0.7-4.0)	72.4 (40)	1110 (16)	79.9 (25)	794 (16)	5490 (38)	6.8 (49)
50 tab	5	0.7 (0.5-1.5)	250 (47)	1930 (26)	75.9 (6)	912 (26)	5990 (27)	9.4 (44)
100 tab	8	1.7 (0.5-3.0)	758 (39)	5690 (21)	143 (20)	620 (21)	7670 (18)	18.2 (26)
100 PIB	8	2.5 (0.5-6.0)	311 (58)	3770 (29)	132 (29)	938 (29)	10700 (45)	13.2 (48)
200 tab	6	1.1 (0.5-2.0)	1440 (26)	10700 (17)	172 (43)	659 (17)	9830 (52)	21.1 (23)
400 tab	5	3.0 (0.7-4.0)	3280 (37)	27700 (36)	184 (51)	509 (36)	8090 (45)	30.4 (20)
600 tab	6	2.2 (0.7-3.0)	4340 (32)	39600 (20)	128 (41)	535 (20)	5920 (58)	32.7 (13)

*gMean= geometric mean, *gCV%=geometric CV%, † fe_{0-tz}=fraction eliminated renally
£PIB=powder-in-bottle formulation, €tab=tablet formulation

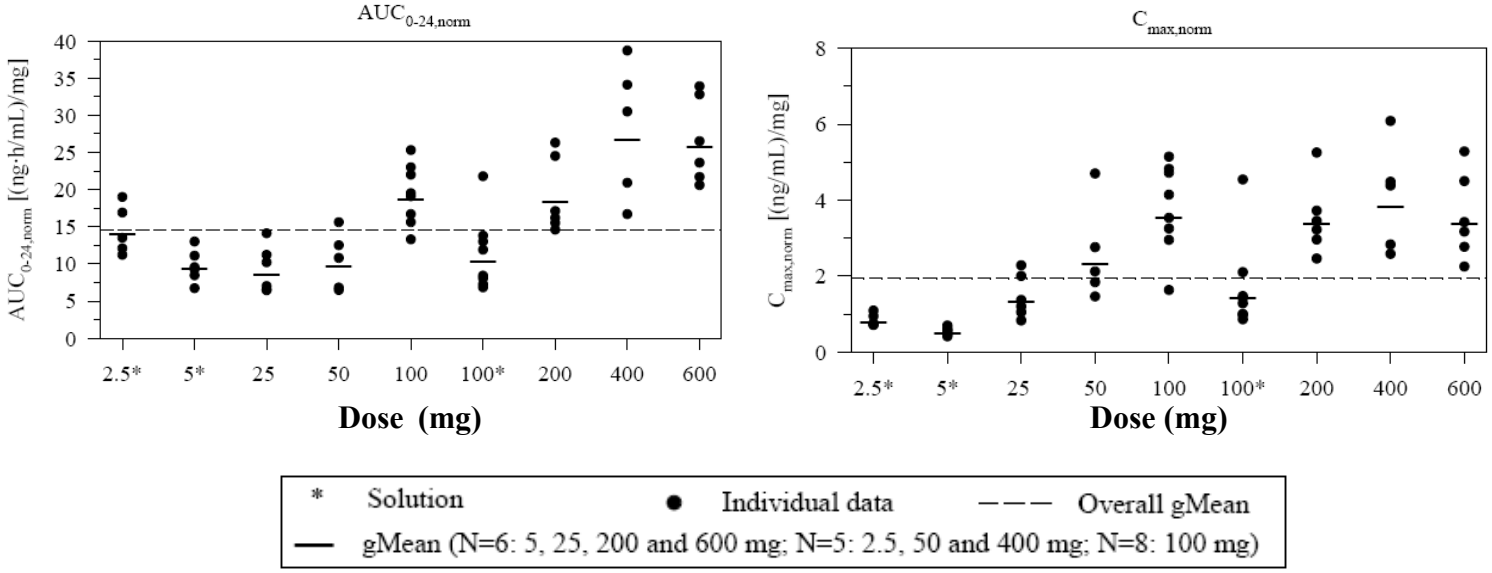


Figure 4: Dose normalized AUC values of linagliptin (BI 1356 BS) after single oral administration of doses ranging from 2.5 mg to 600 mg in single rising dose trial 1218.1

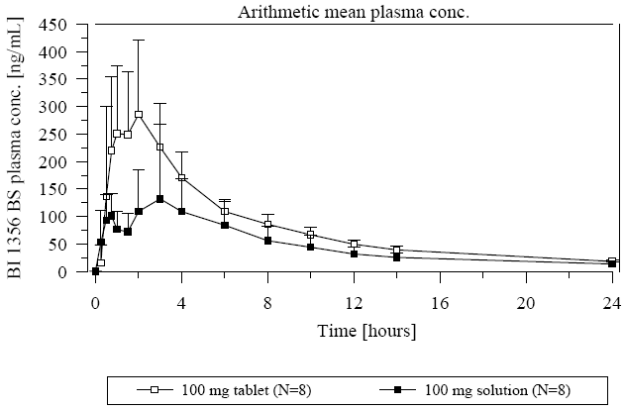


Figure 5: Arithmetic mean drug plasma concentration-time profiles (+ SD) of linagliptin after single oral administration of 100 mg linagliptin tablet and solution (PIB) (time axis reduced to first 24 h after drug administration)

- **Conclusions:**
  - This study explored a wide range of linagliptin doses ranging from 2.5 mg to 600 mg while the proposed therapeutic dose is 5 mg. There were no serious adverse events reported; thus, this study establishes a large safety margin for single-dose exposures.
  - In this study sponsor found out that their target of >80% inhibition of DPP-4 was already achieved at lower doses; therefore only dose up to 10 mg were evaluated in all other clinical trials, except the QT study which also evaluated a supratherapeutic dose of 100 mg.
  - This trial informs us about the following PK behavior of linagliptin: less than dose-proportional increase in exposure for 1 to 10 mg dose (likely because of concentration dependent binding to DPP-4), more than dose-proportional increase in exposure for 25 to

100 mg dose (likely because of inhibition of P-gp and CYP 3A4 at higher concentrations), and almost dose-proportional increase in exposure for 100 to 600 mg dose (likely because of saturation of P-gp and CYP 3A4 inhibitory effect at further high concentrations).

- The lower exposures for solution compared to tablet formulation may have implications for development of pediatric formulation. However, the 100 mg dose is supratherapeutic and exposures for these formulations need to be compared at therapeutically relevant doses.

3 Single Rising Dose (IV)

Trial # 1218.10

Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses (0.5 mg to 10 mg) of linagliptin as formulation for intravenous administration in healthy male volunteers.

- **Objective:** To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of linagliptin as formulation for intravenous administration
- **Study design:** Randomized, placebo controlled and single-blind within dose groups, single rising dose, including a crossover intra-individual bioavailability comparison of intravenous solution (5 mg) and tablet (10 mg)
- **Test drug and sample size:** 0.5 mg (N=6), 2.5 mg (N=6), 5 mg (N=10) and 10 mg linagliptin (N=6) as intravenous infusion (solution: linagliptin 10 mg /20 mL diluted in 0.9% NaCl) and 10 mg as tablet (N=10)
- **Results:**
  - The PK parameters from this study are listed in Table 11. The non-linear PK behavior was observed for IV data (see Table 12 and Figure 6 for results of dose proportionality analysis), which was consistent with the observation for oral administration (in trial 1218.1).
  - The observed data from IV and oral route were modeled with a three compartment model accounting for concentration dependent binding of linagliptin to DPP-4 to predict the absolute bioavailability, which was estimated to be 29.5% with high interindividual variability of 46.7%.

Table 11: Key pharmacokinetic parameters of linagliptin after single intravenous infusion or oral administration of 0.5 mg and 10 mg doses

Dose[†] (mg)	N	T_{max} (hr) Median (range)	gMean (gCV%)[*]				
			C_{max} (nM)	$AUC_{0-\infty}$ (nM hr)	$t_{1/2}$ (h)	CL[£] (mL/min)	V_z[€] (L)
0.5 iv	6	1.50 (1.50-1.53)	11.7 (19)	422 (25)	126 (21)	41.8 (25)	456 (19)
2.5 iv	6	1.50 (1.50-1.53)	48.6 (24)	821 (26)	139 (19)	107 (26)	1300 (18)
5 iv	10	1.50 (1.50-1.53)	90.9 (15)	1250 (18)	127 (19)	141 (18)	1550 (15)
10 iv	6	1.25 (1.00-1.53)	176.0 (23)	1480 (7)	127 (11)	239 (6)	2620 (11)
10 po	10	3.00 (0.50-4.00)	21.0 (73)	1010 (32)	116 (18)	349 (32)	3520 (27)

Table 12: Results of the dose proportionality analysis of the pharmacokinetic parameters after IV infusion of 0.5 to 10 mg linagliptin

Parameter	N	Point estimate	L 95%CI	U 95% CI
AUC0-∞ (nM•h)	28	0.439	0.365	0.513
AUC0-tz (nM•h)	28	0.475	0.416	0.534

Cmax (nM)	28	0.898	0.829	0.967

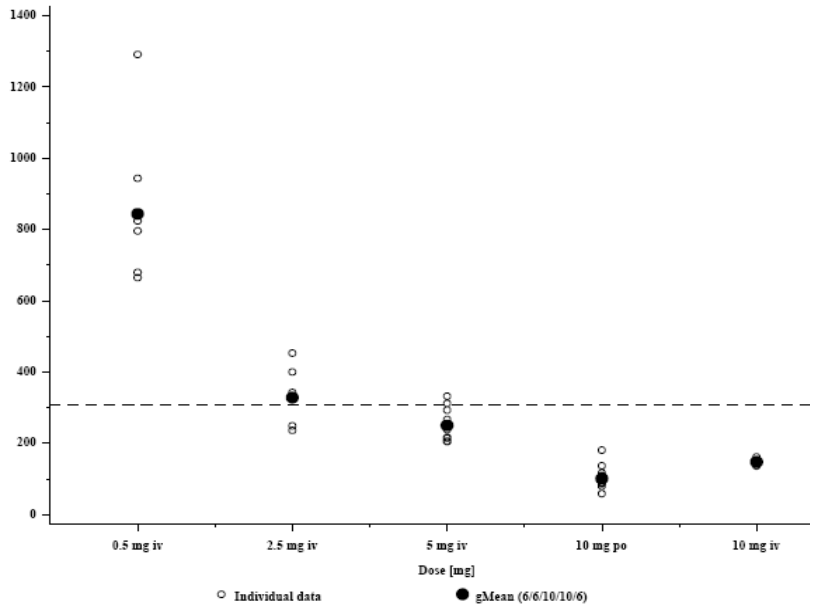


Figure 6: Dose normalized AUC values of linagliptin (BI 1356 BS) after administration of single IV infusion or oral tablet for doses ranging from 0.5 mg to 10 mg in a single rising dose trial 1218.10

- **Conclusions:**
  - Less than dose-proportional increase in exposure for dose range 1 to 10 mg was consistent for both oral and IV route.
  - Geometric CV% on AUC after IV administration was low (<30%), indicating to low inherent between subject variability in linagliptin PK. The variability remained low for oral route, suggesting that formulation did not have any significant effect on variability.

4 Multiple Rising Dose (12 days)

Trial # 1218.2

Title: Safety, tolerability, pharmacokinetics and pharmacodymamics of multiple rising oral doses (1, 2.5, 5, and 10 mg q.d. for 12 days) of linagliptin as powder in the bottle (PIB) in patients with type 2 diabetes

- **Objective:** To investigate safety, tolerability, pharmacokinetics and pharmacodynamics of linagliptin after multiple doses
- **Study design:** Randomized, double-blind within dose group, placebo controlled
- **Test drug and sample size:** 1 mg, 2.5 mg, 5 mg, and 10 mg linagliptin as PIB formulation. N=6 in each group.
- **Results:**
  - Linagliptin PK behavior after multiple doses was consistent with that observed after single-dose (i.e., non-linear PK; Table 13 and Figure 7).

- The terminal half-life was long (>100 hrs) but accumulation was reached within 4-7 days. Based on accumulation ratio, the effective half-life ranged from 9 to 24 hrs for 10 to 1 mg dose (calculated as $t_{1/2,\ accumulation} = \tau.\ln 2/\ln(R_{A,AUC}/(R_{A,AUC}-1))$.
- With 5 mg and 10 mg doses DPP-4 inhibition of 80% at 24hr post-dose was achieved as early as day 2 (Figure 8). For 2.5 mg dose it takes longer time to achieve that DPP-4 inhibition target.

Table 13: Key pharmacokinetic parameters after multiple oral administration of 1 mg to 10 mg linagliptin in a 12-day long study 1218.2

Dose (mg)	N	T_{max} (hr) Median (range)	gMean (gCV%)*								
			Single-dose		Steady-state (day 12)					Accumulation	
			C_{max} (nM)	AUC_{0-24} (nM hr)	$C_{max,ss}$ (nM)	$AUC_{\tau,ss}$ (nM hr)	$t_{1/2,ss}$ (h)	$CL/F_{,ss}$ (mL/min)	$V_z/F_{,ss}$ (L)	$R_{A,Cmax}$	$R_{A,AUC}$
1	6	1.5 (1-3)	3.1 (43)	40.2 (40)	4.5 (29)	81.7 (28)	121 (21)	431 (28)	4510 (32)	1.44 (26)	2.03 (31)
2.5	6	2.0 (1-3)	5.3 (25)	85.3 (23)	6.6 (23)	117 (16)	113 (10)	757 (16)	7400 (13)	1.25 (11)	1.37 (8)
5	6	1.8 (0.9-6)	8.3 (42)	118 (16)	11.1 (22)	158 (10)	131 (17)	1120 (10)	12700 (18)	1.33 (30)	1.33 (15)
10	6	2 (1.5-6)	6.7 (30)	161 (16)	13.6 (30)	190 (17)	130 (12)	1850 (17)	20800 (23)	1.40 (48)	1.18 (23)

*gMean= geometric mean and gCV%=geometric CV%

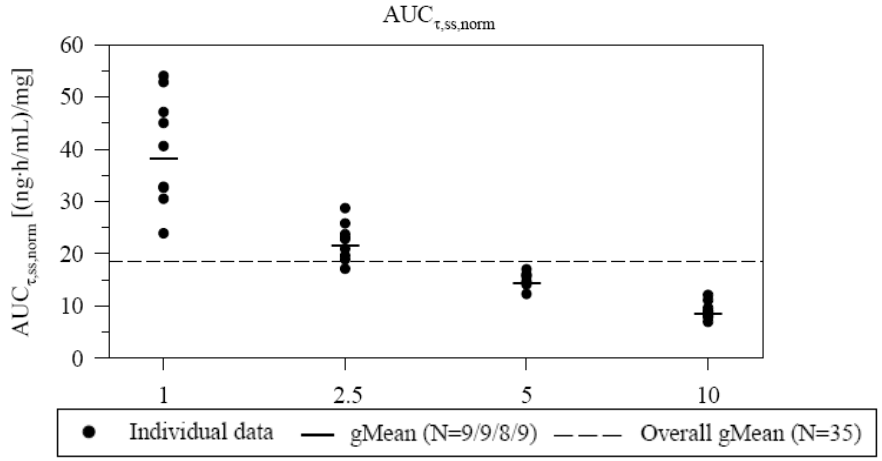


Figure 7: Dose normalized AUC values of linagliptin (BI 1356 BS) at steady-state after oral administration of doses ranging from 1 mg to 10 mg in multiple rising dose trial 1218.2

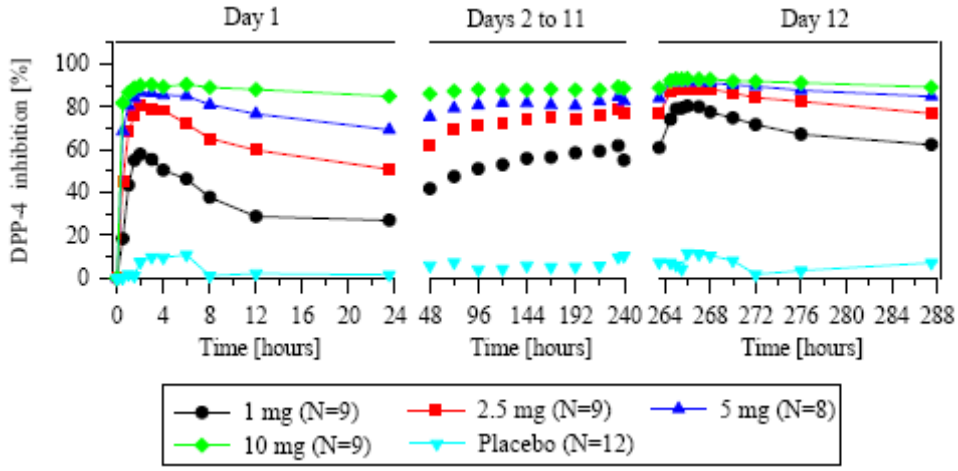


Figure 8: DPP-4 inhibition from baseline induced by linagliptin in the multiple rising dose Phase 1 study 1218.2

- **Conclusions:** Sponsor's preliminary dose selection criteria was to achieve >80% DPP-4 inhibition in more than 80% of patients at steady-state (i.e., at 24th hr post-dose), which was met with doses of 5 mg and above. In this study average steady-state DPP-4 inhibition with 2.5 mg dose was lower than 80%; however, based on Figure 8, even 2.5 mg dose may meet DPP-4 inhibition criteria after administration for relatively longer duration.

5 Multiple Rising Dose (28 days)

Trial # 1218.3

Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple oral doses (2.5, 5, and 10 mg q.d. for 28 days) of linagliptin as tablet in patients with type 2 diabetes

- **Objective:** To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of linagliptin during 4 week treatment duration
- **Study design:** Randomized, double-blind within dose group, placebo controlled, multiple doses in male and female patients
- **Test drug and sample size:** 2.5 mg Linagliptin – 26 patients, 5 mg Linagliptin – 16 patients, 10 mg Linagliptin – 19 patients, placebo – 16 patients
- **Results:** PK parameters from this trial are listed in Table 14 and estimates of DPP-4 activity on day 1 and day 28 are shown in Table 15. PK characteristics were similar to that reported in trial 1218.2. Assessment of dose proportionality suggested non-linear PK with the following point estimate (95%CI) for slope of relationship between PK parameters and dose: $AUC_{\tau,ss}$= 0.41 (0.32-0.51), $C_{max,ss}$= 0.67 (0.50 – 0.84), and trough concentrations ($C_{pre,ss}$) = 0.25 (0.16-0.34).

  Steady-state DPP-4 inhibition of >80% was achieved with all three tested linagliptin doses, with median DPP-4 inhibition of 81, 88, and 90% for 2.5, 5, and 10 mg doses, respectively. Among other PD markers, GLP-1 plasma concentrations were measured, which were

expected to rise following inhibition of DPP-4 (mechanistically). GLP-1 concentrations after 5 and 10 mg doses increased by ~3 fold compared to placebo (Table 16), but because of large variability this difference was not statistically significant.

Table 14: Key pharmacokinetic parameters after multiple oral administration of 2.5 mg to 10 mg linagliptin in a four-week long study 1218.3

Dose (mg)	N	T_{max} (hr) Median (range)	gMean (gCV%)*								
			Single-dose		Steady-state (day 28)					Accumulation	
			C_{max} (nM)	AUC_{0-24} (nM hr)	$C_{max,ss}$ (nM)	$AUC_{\tau,ss}$ (nM hr)	$t_{1/2,ss}$ (h)	$CL/F_{,ss}$ (mL/min)	$V_z/F_{,ss}$ (L)	$R_{A,Cmax}$	$R_{A,AUC}$
2.5	26	1.5	6.1	93.1	7.4	116	183	785	12000	1.22	1.25
		(0.5-8.0)	(42)	(28)	(28)	(21)	(21)	(21)	(28)	(34)	(19)
5	15	2.0	9.6	124	12.3	148	194	1190	20000	1.29	1.20
		(1.0-6.2)	(39)	(20)	(40)	(19)	(15)	(19)	(29)	(41)	(20)
10	19	1.5	18.8	188	18.6	207	203	1700	30000	0.99	1.10
		(1.0-8.0)	(65)	(33)	(56)	(27)	(16)	(27)	(25)	(87)	(30)

Table 15: Geometric mean (%geometric CV) DPP-4 activity on days 1 and 28 after oral administration of 2.5, 5, and 10 mg linagliptin

		Day 1		Day 28	
Dose	N	E_{min} [%]	E_{24} [%]	$E_{min,ss}$ [%]	$E_{\tau,ss}$ [%]
Placebo	16	80.9 (16.2)	94.8 (6.54)	83.7 (15.3)	91.9 (11.0)
2.5 mg	26	13.8 (53.9)	34.8 (39.0)	8.93 (33.3)	18.2 (30.1)
5 mg	15	8.91 (23.3)	18.4 (26.8)	7.92 (20.1)	11.9 (24.5)
10 mg	19	7.12 (23.4)	11.7 (31.4)	6.66 (15.7)	9.61 (17.1)

Table 16: Arithmetic mean (%CV) difference in GLP-1 plasma concentrations measured before and 30 min after MTT on days -1, 1 and 29 after single and multiple administrations of linagliptin or placebo for 28 days

Dose (N per day)	Day -1 [pmol/L]	Day 1 [pmol/L]	Day 29 [pmol/L]
Placebo (N=16)	2.40 (64.5)	1.72 (84.9)	3.61 (202)
2.5 mg BI 1356 BS (N=26)	2.99 (89.3)	6.26 (71.4)	10.7 (129)
5 mg BI 1356 BS (N=16/16/15)	2.38 (141)	5.72 (84.9)	10.7 (167)
10 mg BI 1356 BS (N=19)	1.92 (85.0)	8.32 (143)	7.77 (123)

- **Conclusions:**
  Linagliptin doses of 2.5 mg, 5 mg , and 10 mg shows steady-state DPP-4 inhibition of >80%. These dose levels also increase GLP-1 concentrations compared to placebo.

6 Dose Proportionality

Trial # 1218.33

Title: Assessment of dose proportionality of different dose strengths of linagliptin tablets after oral administration to healthy male and female volunteers in an open, randomized, multiple-dose, three-period crossover, phase I trial

- **Objective:**
  To assess the pharmacokinetics and dose proportionality of 1 mg, 2.5 mg and 5 mg tablets of linagliptin
- **Study design:**
  Open-label, randomized, multiple-dose, three-period cross-over design without wash-out periods between the treatments
- **Treatment groups and sample size:**
  7 days of treatment with each of the following:
  - Linagliptin 1 mg iFF* (intended final formulation), N=12
  - Linagliptin 2.5 mg iFF, N=12
  - Linagliptin 5 mg iFF, N=12

***Note:** - iFF only differed from the final formulation (b) (4)

- **Results:**
  The PK parameters from the iFF of linagliptin are listed in Table 17. In the dose range investigated, linagliptin exhibited nonlinear pharmacokinetics, with a less than proportional increase in $C_{max,ss}$, $AUC_{\tau,ss}$, and $C_{24,ss}$ with increasing doses. The slope (90% CI) of power model was less than 1 for all three PK parameters (Table 18) [power model: PK parameter = intercept • $(Dose)^{slope}$].

Table 17: Main pharmacokinetic parameters of linagliptin after administration of 1 mg, 2.5 mg and 5 mg tablets (iFF)

	1 mg (N=12)		2.5 mg (N=12)		5 mg (N=12)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [nM·h]	86.0	17.0	114	16.2	153	23.7
$AUC_{\tau,ss,norm}$ [(nM·h)/mg]	86.0	17.0	45.7	16.2	30.6	23.7
$C_{max,ss}$ [nM]	4.84	21.2	7.50	23.8	12.9	47.8
$C_{max,ss,norm}$ [(nM)/mg]	4.84	21.2	3.00	23.8	2.57	47.8
$t_{max,ss}$[1] [h]	1.51	0.500-6.00	1.01	0.500-3.00	1.27	1.00-4.00
$C_{24,ss}$[nmol/L]	2.92	21.6	3.92	18.4	4.90	22.5

[1] median and range given

Table 18: Slope for the power model of the logarithmic pharmacokinetic endpoints $AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{24,ss}$ of linagliptin

Parameter	Point Estimator	Lower Limit of 95% CI	Upper Limit of 95% CI
$AUC_{\tau,ss}$	0.3561	0.3135	0.3986
$C_{max,ss}$	0.5999	0.5010	0.6988
$C_{24,ss}$	0.3228	0.2840	0.3616

- **Conclusion**

Linagliptin exposures increase in less than dose-proportional manner in the dose range of 1 mg to 5 mg.

7 Comparison of 2.5 mg bid vs. 5 mg qd

Trial # 1218.45

Title: Pharmacokinetics and pharmacodynamics of multiple 5 mg doses of linagliptin p.o. given once daily compared to multiple 2.5 mg doses given twice daily in healthy male and female volunteers.

- **Objective:** 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 linagliptin
- **Study design:**
  - An open-label, multiple-dose, two-way crossover design
  - The duration of each of the 2 treatment periods was 7 days. The treatment periods were not separated by a wash-out period.
- **Treatment groups and sample size:**
  - Treatment A: 5 mg linagliptin once daily, N=15
  - Treatment B: 2.5 mg linagliptin twice daily, N=15
- **Results:**
  The steady-state exposures for both dosing regimens were comparable (Table 19). The geometric mean ratio and 90% CI for comparison of $AUC_{0-24,ss}$ between two dosing regimens were in the range of 80% to 125%, which is also the usual criteria for bioequivalence assessment. For both dosing regimens mean plasma DPP-4 inhibition was ≥80% over the dosing intervals of 12 and 24 hrs.

Table 19: Comparison of pharmacokinetic parameters of linagliptin by treatment over 24 h

		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.

Table 20: Comparison and 90% confidence interval of the pharmacokinetic parameter $AUC_{0-24,ss}$ between the different dosage regimens based on the PK set

Parameter	N	Test	Reference	Intra-individual gCV [%]	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90% confidence interval	
						Lower limit [%]	Upper limit [%]
$AUC_{0-24,ss}$ [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

- **Conclusion**
  The 2.5 mg bid and 5 mg qd dosing regimens are comparable in terms of steady-state PK and mean DPP-4 inhibition

SPECIFIC POPULATION

8 Renal impairment (PK study)

Trial # 1218.26

Title: Pharmacokinetics, pharmacodynamics, safety and tolerability of single and multiple 5 mg doses of linagliptin tablets in patients with different degrees of renal impairment in comparison to subjects with normal renal function in an open, parallel-group, phase I trial

- **Objective:** To assess the effect of different degrees of renal impairment (RI) on the safety, pharmacokinetics, and pharmacodynamics of orally administered linagliptin.
- **Study design:** Open-label, parallel-group phase I trial
- **Treatment groups and sample size:**
  Patients were allocated to renal function groups by rate of creatinine clearance (CrCl), as follows:
  - Group 1 (non-diabetic subjects with normal renal function): (CrCl)>80 mL/min, N=6
  - Group 2 (non-diabetic patients with mild RI): CrCl>50 to ≤80 mL/min, N=6
  - Group 3 (non-diabetic patients with moderate RI): CrCl>30 to ≤50 mL/min, N=6
  - Group 4 (non-diabetic patients with severe RI), CrCl≤30 mL/min, N=6
  - Group 5 (non-diabetic patients with end-stage renal disease; ESRD): CrCl≤30 mL/min and requirement for haemodialysis, N=6

  Groups 6 and 7 included only patients with Type 2 diabetes mellitus (T2DM):
  - Group 6 (patients with severe RI and T2DM): CrCl≤30 mL/min, N=10
  - Group 7 (patients with normal renal function and T2DM): CrCl>80 mL/min, N=11
- **Duration of Treatment:**
  Groups 1, 2 and 3: once daily for 7 days (multiple dose)
  Groups 4 and 5: once daily for 1 day (single dose)
  Groups 6 and 7: once daily for 10 days (multiple dose)
- **Results:**
  - Linagliptin exposures increased by 55-70% in patients with moderate and severe RI compared to patients with normal renal function. The single-dose and steady-state PK parameters for different patients groups are listed in Table 21 and Table 22, respectively, and geometric mean ratios (90%CI) for comparison against respective control group is shown in Figure 9.
  - Renal excretion ($fe_{0-24,ss}$ in Table 22) of linagliptin was <7% of the administered dose under steady-state conditions.
  - The exposures were relatively higher for creatinine clearance <60 (Figure 10).
  - Renal impairment did not alter the plasma protein binding.

Table 21: Geometric mean (%gCV) single dose noncompartmental PK parameters of linagliptin after oral administration of a single dose of 5 mg linagliptin

Group	normal RF		mild RI		moderate RI		severe RI		ESRD		severe RI +T2DM		normal RF +T2DM	
N	6		6		6		6		6		10		11	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-24} [nmol·h/L]	101	32.6	130	11.0	158	44.3	142	26.3	155	16.8	155	50.3	127	25.3
C_{max} [nmol/L]	7.32	62.7	9.20	18.1	11.5	89.1	10.8	55.0	11.0	28.6	12.2	74.2	10.0	41.1
t_{max}* [h]	2.25	0.500-8.00	1.50	0.500-3.03	2.25	0.750-4.00	1.50	0.750-3.00	3.00	1.00-4.00	1.50	0.750-4.02	3.00	0.500-4.00
C_{24} [nmol/L]	3.59	33.8	4.66	24.7	4.85	18.8	4.61	23.3	5.32	16.0	4.88	43.9	4.12	25.3
fe_{0-24} [%]	0.232	183	0.332	117	0.368	391	0.308	104	---	---	0.530	140	0.935	156
$CL_{R,0-24}$ [mL/min]	4.06	119	4.50	132	4.12	208	3.83	77.0	---	---	6.02	74.6	13.0	130
$t_{½}$ [h]	---	---	---	---	---	---	133	51.0	129	21.7	---	---	---	---

* for $t_{max,ss}$, the median and range (min-max) is given

Table 22: Geometric mean (%gCV) steady state noncompartmental PK parameters of linagliptin after oral administration of multiple 5 mg doses

Group	normal RF		mild RI		moderate RI		severe RI+T2DM		normal RF+T2DM	
N	6		6		6		10		11	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [nmol·h/L]	154	21.2	166	10.3	263	25.6	262	43.8	185	22.8
$C_{max,ss}$ [nmol/L]	13.2	38.9	12.9	24.5	19.3	41.3	22.6	60.8	16.7	32.1
$t_{max,ss}$* [h]	0.517	0.500-1.50	2.50	0.533-3.10	1.27	0.750-3.00	1.26	0.750- 2.00	1.00	0.500- 3.00
$C_{24,ss}$ [nmol/L]	5.13	16.9	5.36	12.1	7.91	20.6	7.24	46.7	5.70	25.5
$t_{1/2,ss}$ [h]	192	31.4	233	17.6	190	32.5	165	56.6	179	47.2
Accumulation, $t_{1/2}$ [h]	15.2	32.0	10.1	42.1	15.9	88.1	17.7	44.3	13.6	38.3
CL/F_{ss} [mL/min]	1150	21.2	1060	10.3	672	25.6	673	43.8	954	22.8
Vz/F_{ss} [L]	19000	41.5	20500	22.2	11000	37.7	9630	81.9	14800	66.9
$MRT_{po,ss}$ [h]	145	17.4	158	18.5	119	16.8	111	33.5	112	23.2
$fe_{0-24,ss}$ [%]	4.26	60.8	3.71	41.2	4.03	47.7	2.68	78.4	6.45	36.4
$CL_{R,0-24,ss}$ [mL/min]	48.9	40.3	39.4	38.6	27.1	24.2	18.1	43.2	61.5	35.6
$R_{A,AUC0-24}$	1.52	15.6	1.27	14.1	1.66	31.9	1.69	22.5	1.45	18.3
$R_{A,Cmax}$	1.81	37.4	1.40	28.3	1.68	63.8	1.85	31.2	1.67	30.2

* for $t_{max,ss}$, the median and range (min-max) is given

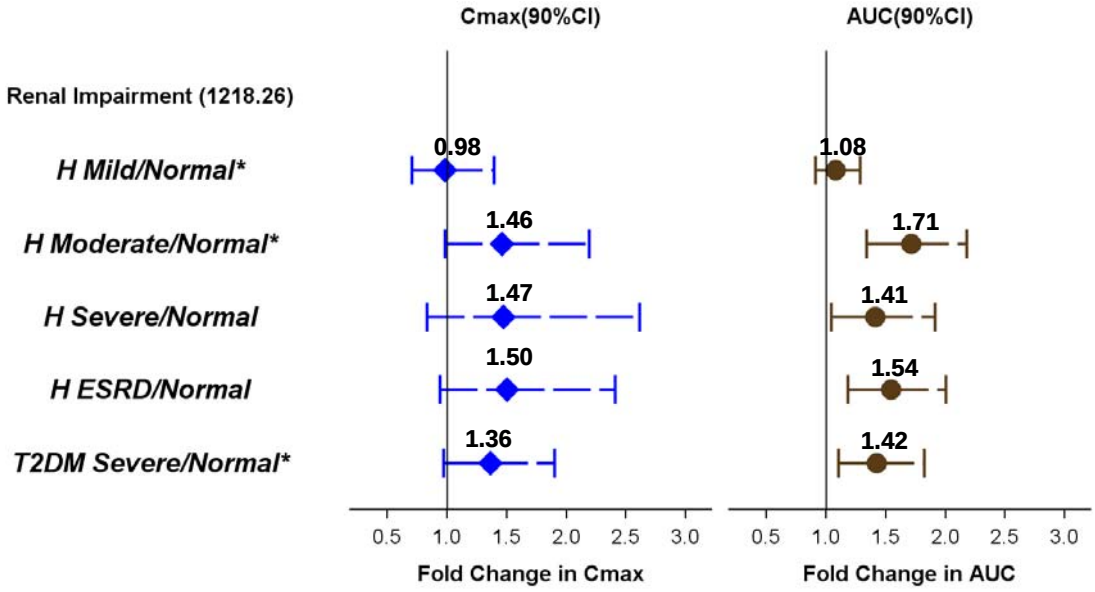


Figure 9: Forest plot demonstrating the relative bioavailability of linagliptin after single and/or multiple oral administration of 5 mg linagliptin to renally impaired subjects compared to control subjects with normal renal function

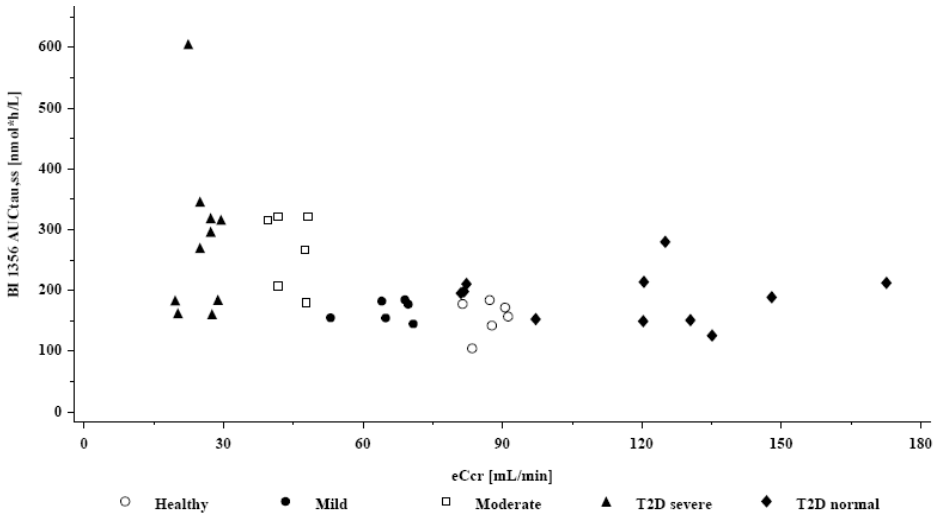


Figure 10: Scatter plot of CrCl (eCcr) and steady state $AUC_{\tau,ss}$ of linagliptin after oral administration of multiple 5 mg doses to subjects with normal renal function, patients with mild or moderate renal impairment, patients with T2DM and severe renal impairment

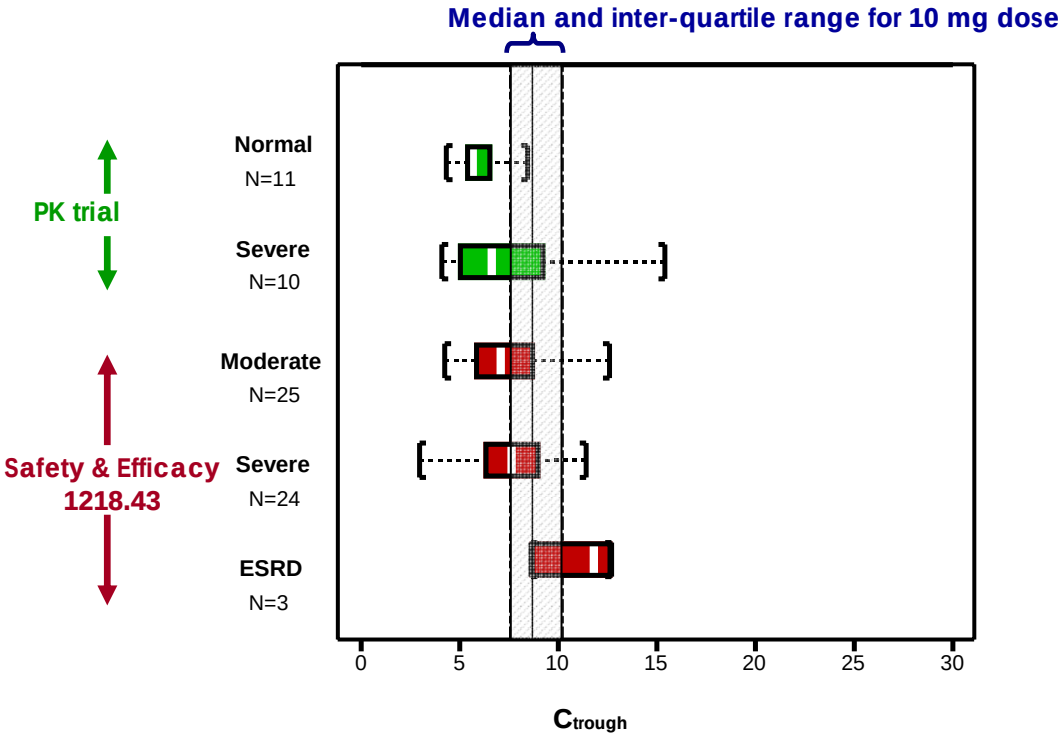


Figure 11: Box plot for comparison of trough concentrations in type 2 diabetic patients from PK renal impairment study 1218.26 and safety and efficacy trial in patients with renal impairment 1218.43. The shaded area shows the median and inter-quartile range for trough concentrations from 10 mg dose in Phase 3 trial in Japanese patients (# 1218.20)

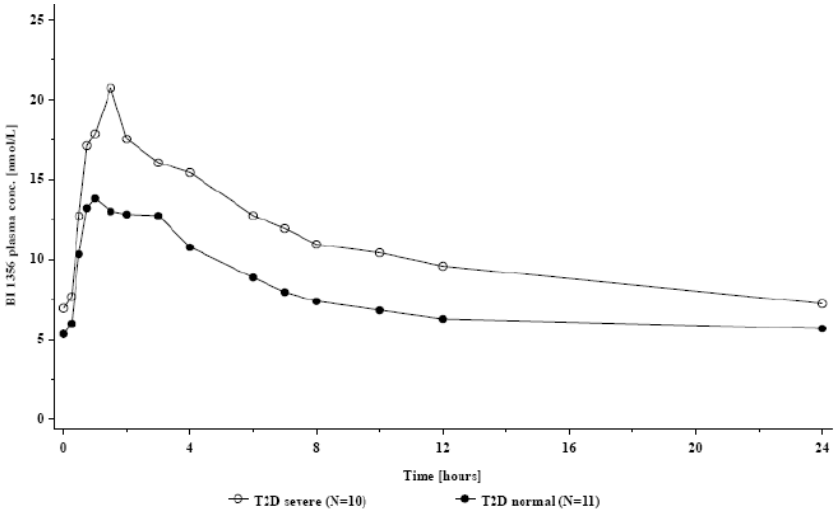


Figure 12: Geometric mean drug plasma concentration-time profiles of linagliptin (BI 1356) at steady state after oral administration of multiple 5 mg doses to patients with T2DM and normal renal function (Group 7) or patients with T2DM and severe RI (Group 6) (Linear scale)

- **Conclusions:**

- In addition to this PK trial patients with RI, sponsor is also conducting a 52 weeks, double-blind, placebo-controlled, safety and efficacy trial in type 2 diabetic patients with severe chronic RI evaluating linagliptin as add-on to pre-existing antidiabetic therapy (Trial # 1218.43). Results from 12-week interim analysis, including safety data and trough concentrations, have been submitted.

- In patients with severe RI and type 2 diabetes (group 6), one patient (#611) had considerably higher plasma concentrations compared to others ($C_{max,ss}$ of 81 nM vs. 9.7-30.6 nM). This patient was receiving 12 comedications and had 13 reported comorbidities. However, none of these comedications or comorbidities were unique to this patient. Other patients were also receiving one or more of these comedications and they also had similar comorbidities. We also compared other available baseline information (e.g., demographics) between these patients but could not find any particular factor to explain higher concentrations in patient # 611.

  To further evaluate whether mean concentrations in type 2 diabetic patients with severe RI were representative of a larger population or were inflated by patient 611, we compared the trough concentrations (C_{trough}) in patients with RI from PK trial (trial #1218.26) with C_{trough} from safety and efficacy trial in patients with moderate and severe RI (trial #1218.43) (Figure 11). C_{trough} in patients with severe RI between these trials were comparable, confirming that linagliptin concentrations increased in patients with renal impairment.

- No linagliptin dose adjustments are recommended for patients with RI. Because higher exposures (as 10 mg dose) have been evaluated in Phase 3 trial, for which no significant safety findings have been reported. Also, 12 week interim-analysis from safety and efficacy trial in renally impaired patients (trial 1218.43) did not find any significant safety issues. In addition, no trend of increase in exposure or trough concentration was noted for decline in renal function from moderate to severe RI (Table 21, Table 22, and Figure 11).

- Comparison of plasma concentration – time profiles between type 2 diabetic patients with severe RI and normal renal function (Figure 12) shows that exposure increases within the 1-4 hours after the first dose and subsequent decline in concentrations remain parallel, indicating to possible changes in absorption and/or pre-systemic metabolism.

9 Hepatic impairment

Trial # 1218.27

Title: Pharmacokinetics and pharmacodynamics of linagliptin 5 mg once daily in male and female subjects with different degrees of liver impairment (Child Pugh classification A-C) as compared to male and female healthy subjects (a non-blinded, parallel group study of phase I)

- **Objective:** To investigate the influence of mild, moderate, and severe liver impairment on the pharmacokinetics and pharmacodynamics of linagliptin in comparison with a control group

with normal hepatic function after single or multiple oral administration of 5 mg linagliptin tablets

- **Study design:** Open-label, parallel-group comparison study
- **Treatment groups and sample size:**
  - Healthy controls (N=8): healthy subjects with normal liver function matched with regard to age, weight, and sex, at least 3 males and 3 females
  - Mild liver impairment (N=8): patients with Child-Pugh class A (6 points), at least 3 males and 3 females
  - Moderate liver impairment (N=8): patients with Child-Pugh class B (7 to 9 points), at least 3 males and 3 females
  - Severe liver impairment (N=8): patients with Child-Pugh class C (10 to 15 points)
- **Treatment duration:**
  - Healthy controls and patients with mild and moderate hepatic impairment: 7 days
  - Patients with severe hepatic impairment: 1 day (single dose)
- **Results:** The single-dose and steady-state PK parameters for patients groups with different degree of hepatic impairment are listed in Table 23 and Table 24, respectively, and geometric mean ratios (90%CI) for comparison against respective control group is shown in Figure 13.

Table 23: Non-compartmental PK parameters of linagliptin after single oral doses of 5 mg linagliptin in patients with different degrees of hepaticimpairment compared with healthy subjects

	Single dose non-compartmental PK parameters of linagliptin							
	Healthy		Mild		Moderate		Severe	
	gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV
N	8		7		9/(7)		8	
AUC_{0-24} [nmol·h/L]	189	27.8	164	33.3	148 (155)	21.3 (17.9)	190	39.4
C_{max} [nmol/L]	17.3	56.9	11.9	45.2	12.1 (12.0)	31.2 (35.8)	13.3	77.8
t_{max}* [h]	1.50	0.500-3.00	1.50	0.250-3.00	1.00 (1.00)	0.250-2.00 (0.250-2.00)	0.875	0.500-6.00
C_{24} [nmol/L]	6.26	24.5	6.45	26.9	5.28 (5.62)	27.0 (19.5)	6.67	23.7
fe_{0-24} [%]	1.31	148	0.705[1]	336	0.483 (0.535)	162 (199)	0.923[2]	275
$CL_{R,0-24}$ [mL/min]	12.2	123	7.31[1]	215	5.75 (6.10)	145 (169)	8.74[2]	161
$t_{½}$ [h]	---	---	---	---	---	---	124	61.2

* for t_{max}, the median and range (min-max) is given
[1] N=6
[2] N=7

Table 24: Steady state non-compartmental PK parameters of linagliptin after multiple oral doses of 5 mg linagliptin to patients with mild or moderate hepatic impairment compared with healthy subjects

	Steady state non-compartmental PK parameters of linagliptin					
	Healthy		Mild		Moderate	
	gMean	gCV	gMean	gCV	gMean	gCV
N	8		8		8 (6)	
$AUC_{\tau,ss}$ [nmol·h/L]	254	18.9	191	27.2	217 (207)	26.0 (25.2)
$C_{max,ss}$ [nmol/L]	20.8	38.6	13.4	55.8	19.2 (17.9)	52.5 (54.2)
$t_{max,ss}$* [h]	1.50	0.500-2.00	1.00	0.500-3.00	0.625 (0.625)	0.250-2.00 (0.250-2.00)
$C_{24,ss}$ [nmol/L]	8.41	18.2	6.75	28.2	7.85 (7.92)	18.8 (13.7)
$t_{1/2,ss}$ [h]	77.7	32.6	95.0	18.0	96.1 (113)	54.7 (36.9)
Accumulation, $t_{1/2}$ [h]	10.9	66.2	8.11[1]	86.8	13.1 (10.8)	61.7 (55.7)
$CL/F_{,ss}$ [mL/min]	696	18.9	922	27.2	813 (852)	26.0 (25.2)
$Vz/F_{,ss}$ [L]	4680	35.7	7580	38.4	6760 (8350)	65.3 (53.0)
$MRT_{po,ss}$ [h]	95.4	23.2	109	27.0	119 (146)	58.9 (41.2)
$fe_{0-24,ss}$ [%]	7.12	50.3	4.84[1]	57.8	6.13 (7.10)	51.2(36.8)
$CL_{R,0-24,ss}$ [mL/min]	49.5	40.8	44.7[1]	40.1	49.8 (60.6)	50.8 (34.3)
$R_{A,AUC0-24}$	1.34	22.2	1.25[1]	23.9	1.46 (1.33)	28.4 (25.3)
$R_{A,Cmax}$	1.20	53.9	1.22[1]	64.3	1.53 (1.43)	65.8 (68.8)

* for $t_{max,ss}$, the median and range (min-max) is given
[1] N=7

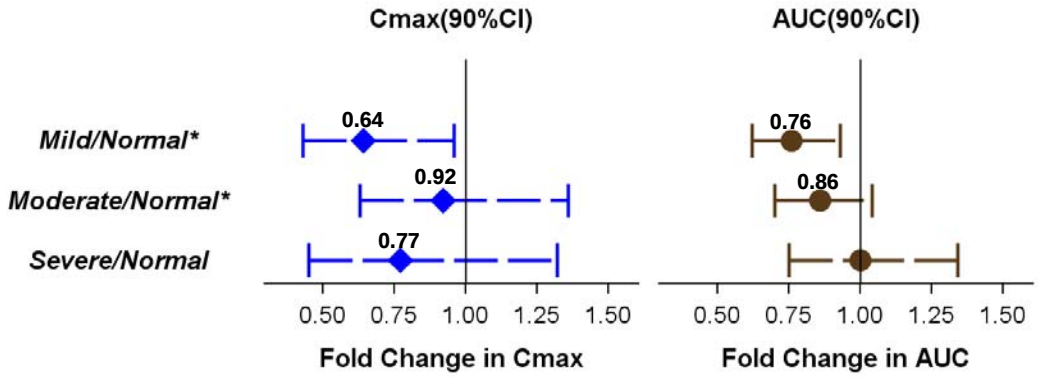


Figure 13: Forest plot demonstrating the relative bioavailability of linagliptin after single and/or multiple oral administration of 5 mg linagliptin to subjects with hepatic impairment or normal renal function

- **Conclusion:**
  These small changes in exposures based on liver function were not clinically meaningful. Therefore, no dose adjustments are recommended for patients with hepatic impairment

10 PK in Japanese Subjects (SRD and 2 Week MRD)

Trial # 1218.11

Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising oral doses (1 to 10 mg) and multiple rising oral doses (2.5 to 10 mg once daily for 12 days) of linagliptin in healthy male volunteers (a randomized, double-blind, placebo-controlled within dose groups clinical trial)

- **Objective:** To examine the safety, tolerability, pharmacokinetics, and pharmacodynamics of linagliptin after oral administration in Japanese healthy subjects
- **Study design:** Randomized, double-blind, placebo-controlled within dose groups at a single centre with single and multiple rising oral doses
  Multiple rising dose treatment followed after the safety of single rising oral dose treatment up to 10 mg was confirmed.
- **Treatment groups and sample size:**
  Single dose treatment (N=32)
  Multiple dose treatment (N=24)
- **Treatments:**
  Single dose treatment: 1 mg, 2.5 mg, 5 mg, and 10 mg
  Multiple dose treatment: 2.5 mg, 5 mg, and 10 mg
- **Results:** The PK in Japanese patients also follows less than proportional behavior in dose range of 1 mg to 10 mg, both after single-dose and at steady-state (Table 25). The steady-state linagliptin exposures in Japanese subjects were higher by approximately 14% for 2.5 mg dose, approximately 25% for 5 mg dose, and approximately 50% for 10 mg dose than that for Caucasian patients (average: ~30% higher exposures). The single-dose and steady-state AUC for 5 mg dose in Japanese subjects were 159 nM•h (71.2 ng/mL x 2.113=159 nM•h, where 2.113 is the conversion factor for ng/mL units to nM units) and 193 nM•h, respectively, while these were about 118 nM•h and 154 nM•h in Caucasian subjects (Table 13, from Multiple Rising Dose (12 days) study). Overall, the pharmacokinetic properties of linagliptin in Japanese subjects such as non-linear pharmacokinetics, a long terminal half-life that is not the accumulation half life, and a dose-dependent but generally low urinary excretion of linagliptin are consistent with previous observations in Caucasians.

Table 25: Pharmacokinetic parameters of linagliptin after multiple oral administration of 2.5, 5 and 10 mg of linagliptin

Multiple, BI 1356 BS			2.5 mg N=6	5 mg N=6	10 mg N=6
Day			gMean (gCV %)	gMean (gCV %)	gMean (gCV %)
1	$AUC_{\tau,1}$	[ng·h/mL]	47.9 (15.6)	71.2 (26.6)	118 (26.9)
	$AUC_{\tau,1,norm}$	[(ng·h/mL)/mg]	19.2 (15.6)	14.2 (26.6)	11.8 (26.9)
	$C_{max,1}$	[ng/mL]	2.62 (13.9)	4.12 (35.3)	8.91 (64.2)
	$C_{max,1,norm}$	[(ng/mL)/mg]	1.05 (13.9)	0.824 (35.3)	0.891 (64.2)
	$t_{max,1}$ [a)]	[h]	3.75 (1.00-6.00)	5.00 (0.500-6.00)	4.50 (1.00-8.00)
	$fe_{0-24,1}$	[%]	0.148 (51.6)	0.606 (274)	3.47 (93.5)
	$CL_{R,0-24,1}$	[mL/min]	1.28 (48.0)	7.09 (186)	49.1 (59.8)
12	$AUC_{\tau,ss}$	[ng·h/mL]	62.8 (13.9)	91.3 (16.2)	135 (10.6)
	$AUC_{\tau,ss,norm}$	[(ng·h/mL)/mg]	25.1 (13.9)	18.3 (16.2)	13.5 (10.6)
	$C_{max,ss}$	[ng/mL]	3.68 (24.3)	5.66 (29.1)	10.3 (17.7)
	$C_{max,ss,norm}$	[(ng/mL)/mg]	1.47 (24.3)	1.13 (29.1)	1.03 (17.7)
	$t_{max,ss}$ [a)]	[h]	3.75 (0.500-6.00)	2.25 (0.500-6.00)	4.00 (1.50-6.00)
	$t_{1/2,ss}$	[h]	142 (7.62)	143 (16.5)	175 (12.5)
	$MRT_{po,ss}$	[h]	130 (4.94)	117 (24.2)	95.5 (11.6)
	$CL/F_{,ss}$	[mL/min]	664 (13.9)	913 (16.2)	1240 (10.6)
	$V_Z/F_{,ss}$	[L]	8180 (16.3)	11300 (21.1)	18700 (16.4)
	$fe_{0-24,ss}$	[%]	4.20 (46.7)	4.88 (60.2)	6.88 (18.8)
	$CL_{R,ss}$	[mL/min]	27.9 (40.3)	44.6 (42.6)	85.0 (16.9)
	$R_{A,AUC}$		1.31 (16.6)	1.28 (14.1)	1.14 (20.6)
	$R_{A,Cmax}$		1.41 (31.1)	1.37 (25.7)	1.16 (48.4)

a): median (min-max)

- **Conclusions:** At 5 mg linagliptin dose exposures in Japanese subjects are ~25% higher than in Caucasians; however, overall PK characteristics are similar between these populations.

11 PK in Japanese Subjects (4 Week MRD)

Trial # 1218.12

Title: A randomized, double-blind, placebo-controlled, multiple dose phase 2 study of linagliptin (0.5 mg, 2.5 mg, and 10 mg in tablet q.d. administered orally for 28 days) to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics in Japanese patients with type 2 diabetes mellitus

- **Objective:** To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of linagliptin (0.5 mg, 2.5 mg, and 10 mg) administered orally once daily for 28 days in Japanese patients with type 2 diabetes mellitus
- **Study design:**
  Randomized, double-blind, placebo-controlled, parallel-group
- **Treatment groups and sample size:**
  0.5 mg, N=19

2.5 mg, N=18
10 mg, N=18
Placebo, N=17

- **Results:** The PK parameters from this trial are listed in Table 26. The PK parameters in type 2 diabetic Japanese patients were similar to that observed in Japanese healthy subjects in trial 1218.11. The exposures of 2.5 mg and 10 mg dose in Japanese patients in this trial were ~40% and ~96% higher, respectively, than the respective exposures in Caucasian patients. However, several patients in this trial were receiving concomitant therapies, which could have also influenced linagliptin exposures by possible interaction with P-gp or CYP 3A4.

Table 26: Pharmacokinetic parameters of linagliptin after multiple oral administration of 0.5, 2.5 or 10 mg of linagliptin once daily for 28 days

Multiple, BI 1356 BS			0.5 mg	2.5 mg	10 mg
Day			gMean (gCV %)	gMean (gCV %)	gMean (gCV %)
1	N		19	18	18
	$AUC_{\tau,1}$	[nmol·h/L]	29.9 (45.7)	129 (23.7)	323 (32.6)
	$AUC_{\tau,1,norm}$	[(nmol·h/L)/mg]	59.7 (45.7)	51.8 (23.7)	32.3 (32.6)
	$C_{max,1}$	[nmol/L]	2.81 (55.4)	8.84 (35.1)	35.1 (80.1)
	$C_{max,1,norm}$	[(nmol/L)/mg]	5.62 (55.4)	3.54 (35.1)	3.51 (80.1)
	$t_{max,1}$ [a)]	[h]	1.50 (1.00-2.00)	1.50 (0.500-8.00)	1.50 (0.500-12.0)
	$fe_{0-24,1}$	[%]	---	0.227 (145)	4.08 (94.7)
	$CL_{R,0-24,1}$	[mL/min]	---	1.54 (120)	44.6 (59.2)
28	N		17	17	18
	$AUC_{\tau,ss}$	[nmol·h/L]	89.4 (27.2)	164 (23.4)	373 (33.5)
	$AUC_{\tau,ss,norm}$	[(nmol·h/L)/mg]	179 (27.2)	65.6 (23.4)	37.3 (33.5)
	$C_{max,ss}$	[nmol/L]	5.02 (33.9)	11.0 (40.9)	44.0 (80.4)
	$C_{max,ss,norm}$	[(nmol/L)/mg]	10.0 (33.9)	4.40 (40.9)	4.40 (80.4)
	$t_{max,ss}$ [a)]	[h]	1.50 (1.00-8.00)	1.50 (0.500-4.00)	1.25 (0.500-2.00)
	$t_{1/2,ss}$	[h]	240 (33.1)	223 (23.0) [b)]	260 (32.3)
	$MRT_{po,ss}$	[h]	214 (16.9)	178 (17.5) [b)]	119 (39.6)
	$CL/F_{,ss}$	[mL/min]	197 (27.2)	537 (23.4)	945 (33.5)
	$V_z/F_{,ss}$	[L]	4090 (45.0)	10400 (31.2) [b)]	21200 (55.5)
	$fe_{0-24,ss}$	[%]	2.26 (93.1) [b)]	4.25 (72.4) [b)]	6.79 (51.6) [c)]
	$CL_{R,ss}$	[mL/min]	4.50 (76.6) [b)]	22.8 (54.7) [b)]	65.0 (30.0) [c)]
	$R_{A,AUC}$		2.88 (28.3)	1.27 (21.4)	1.16 (27.8)
	$R_{A,Cmax}$		1.71 (35.8)	1.23 (40.4)	1.25 (78.0)

---=Not calculated
a) median (min-max)
b) N=16
c) N=17

- **Conclusions:** The linagliptin PK exposures in Japanese patients with type 2 diabetes are higher than that observed in Caucasian patients. However, in this trial most of these patients were receiving concomitant therapies, which may have also affected the exposures by induction/inhibition of P-gp and CYP 3A4 transporters.

12 PK in Chinese subjects (MRD)

Trial # 1218.58

Title: Pharmacokinetics of single and multiple oral doses of 5 mg linagliptin in healthy Chinese volunteers

- **Objective:** To investigate the pharmacokinetics of Linagliptin after single and multiple oral doses of 5 mg in Chinese healthy subjects
- **Study design:** Open-label, single and multiple dose
- **Treatment groups and sample size:**
  6 males and 6 females for both single-dose and steady-state PK
- **Results:** The PK parameters in Chinese subjects are listed in Table 27. The single-dose linagliptin exposures in Chinese subjects were approximately 27% higher than that observed in Caucasian subjects. Peak and total steady-state exposure observed in this study was comparable to data previously observed in Japanese healthy subjects. The pharmacokinetic features of linagliptin such as a low accumulation ratio, a long terminal half-life that does not represent the accumulation half-life of about 11.5 hrs, and a low urinary excretion are consistent with previous observations in Japanese and Caucasian subjects.

Table 27: Geometric mean (%gCV) - single and multiple dose noncompartmental PK parameters of linagliptin after multiple oral administration of 5 mg linagliptin to Chinese healthy volunteers (N=12)

	Unit	gMean	gCV[%]
$AUC_{0-\infty}$	[nmol*h/L]	658	28
AUC_{0-24}	[nmol*h/L]	150	25.3
C_{max}	[nmol/L]	10.4	46
t_{max}*	[h]	1.75	1.50 - 8.00
$t_{1/2}$	[h]	82.4	16.7
Vz/F	[L]	1910	23.5
CL/F	[mL/min]	268	28.0
MRT_{po}	[h]	109	16.0
fe_{0-24}	[%]	1.91	138
fe_{0-168}	[%]	5.11	48.4
CLR_{0-24}	[mL/min]	22.3	109
CLR_{0-144}	[mL/min]	18.3	48.5
$AUC_{\tau,ss}$	[nmol*h/L]	204	24.5
$C_{max,ss}$	[nmol/L]	14.1	49.4
$t_{max,ss}$*	[h]	1.50	0.500 - 4.00
$C_{24,ss}$	[nmol/L]	6.05	17.8
$t_{1/2,ss}$	[h]	103	14.5
$VZ/F_{,ss}$	[L]	7730	24.6
$CL/F_{,ss}$	[mL/min]	866	24.5
$MRT_{po,ss}$	[h]	86.5	23.7
$fe_{0-24,ss}$	[%]	7.86	39.6
$CLR_{0-24,ss}$	[mL/min]	68.1	23.0
$RAAUC_{0-24}$	[.]	1.35	17.8
RAC_{max}	[.]	1.35	38.3
Accumulation $t_{1/2}$	[h]	11.5	46.9

* for t_{max} and $t_{max,SS}$, the median and range (min-max) is given

- **Conclusion:** The single-dose exposures in Chinese subjects were comparable to that observed in Japanese subjects, and both were 25-30% higher than Caucasian subjects.

DRUG-DRUG INTERACTIONS

13 Ritonavir

Trial # 1218.31

Title: Relative bioavailability of a single oral dose of linagliptin (5 mg) after co-administration with multiple oral doses of ritonavir (200 mg bid for 3 days) compared to the bioavailability of a single oral dose of linagliptin (5 mg) alone in healthy male volunteers (an open-label, randomized, two-way crossover, clinical phase I study)

- **Objective:** To investigate the effect of the P-gp and CYP3A4 inhibitor ritonavir on the pharmacokinetics of BI 1356
- **Study design:**
  Open-label, randomized, two-way cross-over
- **Treatment groups and sample size:**
  - **Test (N=12):** 200 mg ritonavir bid for 3 days (days -1 to 2) with a single dose of linagliptin 5 mg on day 1
  - **Reference (N=12):** Single-dose of linagliptin 5 mg on day 1

  Treatment periods were separated by a wash-out duration of at least 35 days.
- **Sampling time points:**
  - Plasma samples for the analysis of linagliptin and CD 1790 were taken up to 96 hours after dosing.
  - Urine was sampled over 24 hours after linagliptin administration.
  - In addition sparse plasma samples for measurements of ritonavir on days 1 to 4 were taken to confirm adequate ritonavir exposures.
- **Results:**
  The linagliptin AUC_{0-24} and C_{max} increased by about 2 and 3 fold following co-administration with ritonavir, respectively, indicating that both rate and extent of absorption were significantly increased. The t_{max} was also reduced with a resulting median value of 1 hr. The geometric mean and 90% CI for comparison of test and reference groups are shown in Table 28 and plasma concentration – time profiles are shown in Figure 14. In combination with ritonavir, renal excretion increased from less than 0.5% to 12.2% of the dose, which was likely because of increase in unbound plasma concentration.

  Administration of ritonavir 200 mg bid for three days (day -1, 1, and 2) resulted in ritonavir geometric mean plasma concentrations of 3580 ng/mL two hours after administration on day 1. IC_{50} of ritonavir for P-gp inhibition was 3.8 μM (=2774 ng/mL) and for CYP 3A4 it was 0.38 μM, therefore, the exposures of ritonavir reached in this study was sufficient to effectively inhibit P-gp and CYP 3A4.

  Sponsor also used the modeling approach to predict the steady-state PK parameters. Based on the model parameters, co-administration with ritonavir resulted in a 4-fold increase in bioavailability and a 16% decrease in clearance.

  The formation of metabolite CD 1790 was almost completely inhibited in all subjects receiving linagliptin with ritonavir, indicating complete inhibition of CYP 3A4 by ritonavir.

Table 28: Statistical analysis of relative bioavailability after oral administration of linagliptin alone or concomitantly with ritonavir

Parameter	Test (N=12)	Reference (N=12)	Ratio T/R (%)	90% CI Lower limit (%)	Upper limit (%)	Intra-ind. gCV (%)
AUC_{0-24}	Linagliptin + Ritonavir	Linagliptin	201.4	185.8	218.3	10.9
C_{max}	Linagliptin + Ritonavir	Linagliptin	295.7	252.0	347.0	21.9

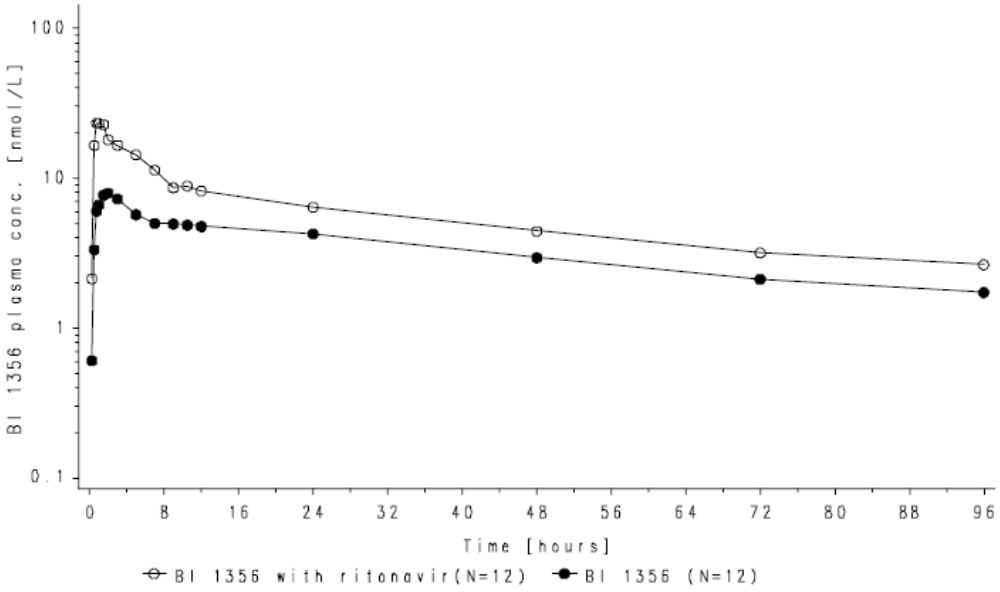


Figure 14: Geometric mean drug plasma concentration-time profiles of linagliptin after single oral admin of 5 mg linagliptin with and without 200 mg ritonavir to healthy male volunteers (semi-log scale)

- **Conclusions:**
  The linaglipitn exposures increased by 2 fold with ritonavir; however, no dose adjustments are recommended because of following reasons: (a) Phase 3 trial 1218.23 tested 10 mg dose in 52 weeks long trial with median C_{trough} ranging between 7.97 to 8.93, while median C_{trough} for 5 mg dose in Phase 3 trials ranged from 5.18 to 5.95 (Trial 1218.20) and 6.29 to 6.56 (Trial 1218.16), indicating that safety and efficacy for almost double exposures were already evaluated, and (b) currently ongoing Phase 3 trial in patients with severe renal impairment (Trial # 1218.43) is also evaluating the safety of higher exposures in a more vulnerable population and no significant safety issues have been reported based on 12-week interim data.

14 Rifampin

Trial # 1218.67

Title: An open-label, 2-period, fixed-sequence, phase I trial to evaluate the effect of multiple doses of rifampin on the multiple-dose pharmacokinetics of linagliptin

- **Objective:** The primary objective was to assess the influence of rifampin, an inducer of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4), on the steady-state pharmacokinetics of linagliptin
- **Study design:**
  Open-label, 2-period, fixed-sequence, multiple-dose trial
- **Treatment groups and sample size:**
  - **Reference (N=16):** linagliptin from Day 1 to Day 12
  - **Test (N=16):** rifampin from Day -6 to Day 6 with administration of linagliptin from Day 1 to Day 6.

  Treatment periods were not separated by a wash-out period. Test treatment was immediately followed by the reference treatment.
- **Sampling time points:**
  - PK/PD samples taken before linagliptin administration on Days 1, 4, 5 (Reference treatment), and on Days 1, 4, 8, 10, 11 (Test treatment).
  - Spot urine samples for determination of 6β-OH cortisol/cortisol ratio were obtained at screening and on Days 1 and 6 of Reference Treatment as well as on Days 4, 6, 8, and 12 of Test Treatment in the morning before drug administration.
- **Results:**
  Co-administration with rifampin significantly reduced linagliptin exposures. The $AUC_{\tau,ss}$ and $C_{max,ss}$ for test and reference treatment and geometric mean ratios for their comparisons are shown in Table 29 and comparison of plasma concentration – time profiles is shown in Figure 15.

  After administration of rifampicin, the 6β-hydroxycortisol to cortisol urine ratio, a marker of CYP3A4 activity, increased by about 5.1-fold and was not influenced by linagliptin administration, indicating adequate CYP3A4 induction

Table 29: Adjusted by-treatment geometric means and relative bioavailability for intraindividual comparisons of $AUC_{\tau,ss}$ and $C_{max,ss}$ of linagliptin after multiple doses of linagliptin 5 mg once daily given alone or concomitantly with multiple doses of rifampicin 600 mg once daily

Parameter	N	Linagliptin and rifampicin (Test)	Linagliptin (Reference)	Adjusted gMean ratio (Test/Reference)	Intra-individual gCV	Two-sided 90% confidence interval	
						Lower limit	Upper limit
		gMean	gMean	[%]	[%]	[%]	[%]
$AUC_{\tau,ss}$ [nmol·h/L]	16	87.6	145	60.5	13.3	55.7	65.7
$C_{max,ss}$ [nmol/L]	16	5.53	9.84	56.2	26.5	47.8	66.0

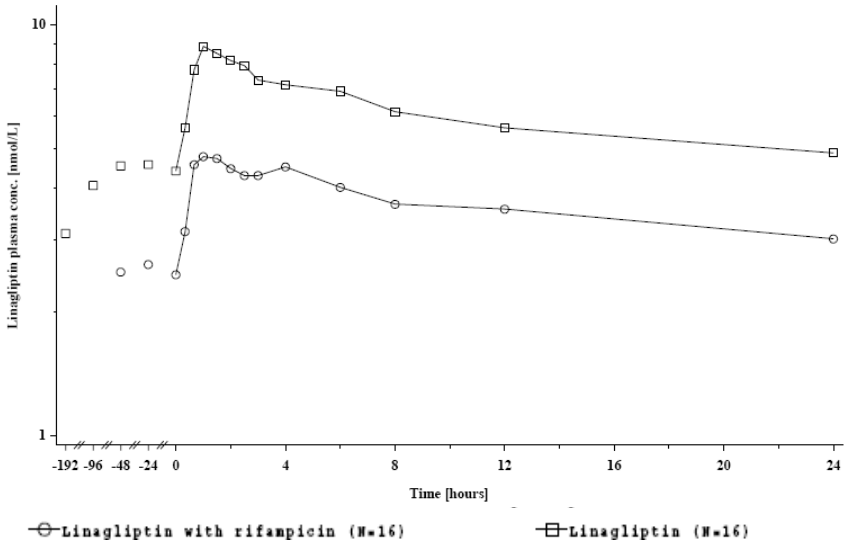


Figure 15: Geometric mean plasma concentration-time profiles (semi-logarithmic scale) of linagliptin after multiple oral administration of 5 mg linagliptin combination with multiple oral doses of 600 once daily alone or in combination with multiple oral doses of 600 mg rifampicin once daily

- **Conclusions:**
  Following co-administration with rifampin, linagliptin exposures declined to the level of 1 mg dose. The 1 mg dose is subtherapeutic and efficacy will be reduced in patients taking linagliptin with CYP 3A4 and P-gp inducers. Therefore, this reviewer recommends use of alternative treatments when linagliptin is to be co-administered with P-gp or CYP 3A4 inducers.

15 Metformin

Trial # 1218.4

Title: Bioavailability of both linagliptin and metformin after co-administration compared to the bioavailability of multiple oral doses of linagliptin 10 mg daily alone and metformin 850 mg three times a day alone in healthy male volunteers

- **Objective:** Investigate the bioavailability of linagliptin and of metformin after concomitant multiple oral administration of 10 mg linagliptin tablets and 3 x 850 mg metformin in comparison to linagliptin and metformin given alone
- **Study design:**
  Open-label, randomized, multiple dose, crossover study with the treatment periods separated by a sufficient wash-out phase.
- **Treatment groups and sample size:**
  - **Treatment A:** Metformin alone for 3 days
  - **Treatment B:** Linagliptin for 6 days alone followed by co administration of metformin for additional 3 days.

Sequence AB: N=6
Sequence BA: N=8

There was a washout period of 2 days (48 hours) between Treatment A and Treatment B (in this order) and a washout period of 18 days between Treatment B and Treatment A (in this order).

- **Sampling time points:** The sampling time points for treatment A and B are shown in Table 30 and Table 31.

Table 30: PK sampling schedule for Treatment A (Metformin only)

Treatment Day	Time
1	Pre-dose (baseline) (assigned to a planned time of -00:15)
2	trough PK samples (just before drug administration of the fifth and sixth dose of metformin) (assigned to a planned time of 31:50 and 39:50)
3-5	0:00 (before dosing), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30 3:00, 4:00; 6:00, 8:00, 12:00, 24:00, and 48:00 h after last drug administration (assigned to a planned time of 47:50, 48:15, 48:30, 48:45, 49, 49:30, 50, 50:30, 51, 52, 54, 56, 60, 72, and 96 h after first administration of metformin)

Table 31: PK sampling schedule for Treatment B (Linagliptin in combination with Metformin)

Treatment Day	Time
1	Pre-dose (baseline)(assigned to a planned time of -00:15)
4-5	trough PK sample (just before drug administration) (assigned to a planned time of 71:50 and 95:50 h after first administration of BI 1356 BS)
6	0:00 (before dosing), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30 3:00, 4:00; 6:00, 8:00, and 12:00 h after drug administration (assigned to a planned time of 119:50, 120:15, 120:30, 120:45, 121, 121:30, 122, 122:30, 123, 124, 126, 128, and 132 h after first administration of BI 1356 BS)
7-8	trough PK sample (just before drug administration) (assigned to a planned time of 143:50 and 167:50 h after first administration of BI 1356 BS)
9-11	0:00 (before dosing), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30 3:00, 4:00; 6:00, 8:00, 12:00, 24:00 and 48:00 h after last drug administration (assigned to a planned time of 191:50, 192:15, 192:30, 192:45, 193, 193:30, 194, 194:30, 195, 196, 198, 200, 204, 216, and 240 h after first administration of BI 1356 BS)

- **Results:** There was no clinically meaningful change in linagliptin PK following co-administration with metformin (Table 32). Vice versa, metformin PK was also not affected by co-administration with linagliptin (Table 33).

Table 32: Adjusted geometric mean ratios and confidence intervals for PK parameter at steady state of linagliptin given alone (Reference) or in combination with metformin (Test)

Parameter	N	Test	Reference	Intra-indiv. gCV (%)	Adjusted gMean Ratio (Test/Reference) (%)	Two sided 90 % Confidence Interval	
						Lower limit [%]	Upper limit [%]
$C_{max,ss}$ [ng/mL]	14	BI 1356 BS + metformin	BI 1356 BS alone	27.4	103.44	86.393	123.850
$AUC_{\tau,ss}$ [ng·h/mL]	14	BI 1356 BS + metformin	BI 1356 BS alone	16.8	119.96	107.32	134.10

Table 33: Adjusted geometric mean ratios and confidence intervals for PK parameter at steady state of metformin given alone (Reference) or in combination with linagliptin (Test)

Parameter	N	Test	Reference	Intra-indiv. gCV (%)	Adjusted gMean Ratio (Test/Reference) (%)	Two sided 90 % Confidence Interval	
						Lower limit [%]	Upper limit [%]
$C_{max,ss}$ [ng/mL]	14	Metformin +BI 1356 BS	Metformin alone	18.5	88.63	78.223	100.410
$AUC_{\tau,ss}$ [ng·h/mL]	14	Metformin +BI1356 BS	Metformin alone	18.0	100.81	89.24	113.86

- **Conclusions:**
  - Metformin is a probe substrate for OCT-1
  - No dose adjustment required for substrates of OCT-1 following co-administration with linagliptin
  - Note that this DDI study is conducted at linagliptin dose of 10 mg, which is higher than the to-be-marketed dose of 5 mg. However, there is no reason to believe that the results of DDI at 5 mg dose would be very different from that of 10 mg dose.

16 Pioglitazone

Trial # 1218.13

Title: Relative bioavailability of both linagliptin and pioglitazone after coadministration compared to the bioavailability of multiple oral doses of linagliptin 10 mg qd alone and pioglitazone 45 mg qd alone in healthy male and female volunteers

- **Objective:** To investigate the bioavailability of linagliptin with and without co-administration of pioglitazone and the bioavailability of pioglitazone with and without coadministration of BI 1356
- **Study design:**
  Open-label, randomized, multiple dose, two-way crossover study.
- **Treatment groups and sample size:**
  - **Treatment AB:** 5 days of treatment with 10 mg linagliptin until steady-state followed by combined treatment of linagliptin with 45 mg pioglitazone for 7 days (days 6-12) to reach steady state of pioglitazone

- **Treatment C:** 7 days of treatment with 45 mg of pioglitazone alone.

Washout between treatments for sequence AB_C: minimum 21 days
Washout between treatments for sequence C_AB: minimum 6 days

- **Sampling time points:** The sampling time points for linagliptin in treatments A and B and for pioglitazone and its active metabolites M-III and M-IV in treatments A, B, and C are shown in Table 34, Table 35, and Table 36.

Table 34: Plasma sampling schedule for linagliptin and CD 1750 (treatments A and B)

Day	Time
1	Before (-0:15 h) first administration of BI 1356 (assigned to the planned time point -0:15 hours)
3, 4	Before (- 0:15 h) administration of BI 1356 (assigned to the planned time points 47:45 h and 71:45 hours)
5	Before (-0:15 h), and 0:15 h, 0:30 h, 0:45 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 hours after administration of BI 1356 (assigned to the planned time points 95:45 h, 96:15 h, 96:30 h, 96:45 h, 97 h, 97:30 h, 98 h, 99 h, 100 h, 102 h, 104 h and 108 hours)
6	Before (-0:15 h) administration BI 1356 and pioglitazone (assigned to the planned time point 119:45 hours)
10,11	Before (-0:15 h) administration BI 1356 and pioglitazone (assigned to the planned time points 215:45 h and 239:45 hours)
12	Before (-0:15 h), and 0:15 h, 0:30 h, 0:45 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 hours after administration of BI 1356 and pioglitazone (assigned to the planned time points 263:45 h, 264:15 h, 264:30 h, 264:45 h, 265 h, 265:30 h, 266 h, 267 h, 268 h, 270 h, 272 h and 276 hours)
13, 14, 16, 18, 20 and 21	In the morning at 0:00 h (assigned to the planned time points 288 h, 312 h, 360 h, 408 h, 456 h and 480 hours)

Table 35: Plasma sampling schedule for pioglitazone and its active metabolites M-III and M-IV (treatments A and B)

Day	Time
1	Before (-0:15 h) first administration of BI 1356 (assigned to the planned time point -0:15 hours)
6	Before (-0:15 h) administration of BI 1356 and pioglitazone (assigned to the planned time point 119:45 hours)
10,11	Before (-0:15 h) administration of BI 1356 and pioglitazone (assigned to the planned time points 215:45 h and 239:45 hours)
12	Before (-0:15 h), and 0:30 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 hours after administration of BI 1356 and pioglitazone (assigned to the planned time points 263:45 h, 264:30 h, 265 h, 265:30 h, 266 h, 267 h, 268 h, 270 h, 272 h and 276 hours)
13, 14, 16, 18, 20 and 21	in the morning at 0:00 h (assigned to the planned time points 288 h, 312 h, 360 h, 408 h , 456 h and 480 hours)

Table 36: Plasma sampling schedule for pioglitazone and its active metabolites M-III and M-IV (treatment C)

Day	Time
1	Before (-0:15 h) first administration of pioglitazone (assigned to the planned time point -0:15 hours)
5, 6	Before (-0:15 h) administration of pioglitazone (assigned to the planned time points 95:45 h and 119:45 hours)
7	Before (-0:15 h), and 0:30 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 hours after administration of pioglitazone (assigned to the planned time points 143:45 h, 144:30 h, 145 h, 145:30 h, 146 h, 147 h, 148 h, 150 h, 152 h and 156 hours)
8, 9, 10, 11 and 12	in the morning at 0:00 h (assigned to the planned time points 168 h, 192 h, 216 h, 240 h and 264 hours)

- **Results:** Geometric mean ratios and 90% CI for comparison of steady-state AUC and C_{max} for linagliptin and its metabolite and for pioglitazone and its metabolite between test (linagliptin + pioglitazone) and reference (linagliptin) treatments are shown in Table 37. Co-administration of pioglitazone with linagliptin did not significantly affect its exposures and vice versa linagliptin did not affect the exposures of pioglitazone or its metabolites.

Table 37: Adjusted by-treatment geometric means and relative bioavailability of linagliptin, pioglitazone, and their metabolites

Parameter	Test (N=20)	Reference (N=20)	Adjusted gMean Ratio (Test/Reference)	Two-sided 90% confidence interval		Intra-individual gCV
			[%]	Lower limit [%]	Upper limit [%]	[%]
BI 1356						
$AUC_{\tau,ss}$ [nmol•h/L]	BI 1356 + Pio	BI 1356	113.4	103.0	124.9	17.8
$C_{max,ss}$ [nmol/L]	BI 1356 + Pio	BI 1356	107.3	92.3	124.8	28.2
CD 1750						
$AUC_{\tau,ss}$ [nmol•h/L]	BI 1356 + Pio	BI 1356	127.3	111.3	145.6	24.9
$C_{max,ss}$ [nmol/L]	BI 1356 + Pio	BI 1356	113.5	97.1	132.6	29.0
Pioglitazone						
$AUC_{\tau,ss}$ [ng•h/mL]	BI 1356 + Pio	Pioglitazone	94.4	87.1	102.2	14.7
$C_{max,ss}$ [ng/mL]	BI 1356 + Pio	Pioglitazone	85.6	78.1	93.8	16.8
M-III						
$AUC_{\tau,ss}$ [ng•h/mL]	BI 1356 + Pio	Pioglitazone	97.7	91.3	104.4	12.3
$C_{max,ss}$ [ng/mL]	BI 1356 + Pio	Pioglitazone	96.4	86.8	106.9	19.1
M-IV						
$AUC_{\tau,ss}$ [ng•h/mL]	BI 1356 + Pio	Pioglitazone	103.9	97.0	111.3	12.6
$C_{max,ss}$ [ng/mL]	BI 1356 + Pio	Pioglitazone	104.6	97.0	112.8	13.9

- **Conclusions:**
  - Pioglitazone is a probe substrate for CYP 2C8

- No dose adjustment required for substrates of CYP 2C8 following co-administration with linagliptin
- Note that this DDI study is conducted at linagliptin dose of 10 mg, which is higher than the to-be-marketed dose of 5 mg. However, there is no reason to believe that results of DDI at 5 mg dose would be very different from that of 10 mg dose.

17 Glyburide

Trial # 1218.30

Title: Relative bioavailability of linagliptin and glyburide after concomitant administration of multiple oral doses of linagliptin 5 mg once daily and a single oral dose of glyburide 1.75 mg compared with the bioavailability of linagliptin and glyburide after each treatment given alone in healthy male and female volunteers (an open label, randomized, 2-way crossover study of Phase I)

- **Objective:**
  - To investigate the effect of multiple doses of linagliptin on PK, safety, and tolerability of glyburide
  - To investigate the effect of single doses of glyburide on PK, safety, and tolerability of linagliptin
- **Study design:**
  Open label, randomized, 2-way crossover study
- **Treatment groups and sample size:**
  - **Treatment AB:** 5 days of treatment with 5 mg linagliptin followed by combined administration of linagliptin with 1.75 mg glyburide on day 6
  - **Treatment C:** Single dose of glyburide 1.75 mg alone.

  Washout between treatments for sequence AB_C: minimum 35 days
  Washout between treatments for sequence C_AB: minimum 7 days
- **Sampling time points:** The sampling time points for PK of linagliptin and glyburide are shown in Table 38, Table 39, and
- Table 40.

Table 38: Plasma sampling schedule for linagliptin and CD 1750 (Treatments A and B)

Treatment	Day	Time
A	1	Before (-0:15 h) first administration of BI 1356 (assigned to the planned time point -0:15 h)
A	3, 4	Before (- 0:15 h) administration of BI 1356 (assigned to the planned time point 47:45 h and 71:45 h)
A	5	Before (-0:15 h) and 0:15 h, 0:30 h, 0:45 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 h after administration of BI 1356 (assigned to the planned time point 95:45 h, 96:15 h, 96:30 h, 96:45 h, 97:00 h, 97:30 h, 98:00 h, 99:00 h, 100:00 h, 102:00 h, 104:00 h and 108:00 h)
B	1	Before (-0:15 h) and 0:15 h, 0:30 h, 0:45 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 h after administration of BI 1356 and glyburide (assigned to the planned time point -0:15 h, 0:15 h, 0:30 h, 0:45 h, 1:00 h, 1:30 h, 2:00 h, 3:00 h, 4:00 h, 6:00 h, 8:00 h and 12:00 h)
B	2	In the morning (assigned to the planned time point 23:45)

Table 39: Plasma sampling schedule for glyburide (Treatments A and B)

Treatment	Day	Time
A	1	Before (-0:15 h) first administration of BI 1356 (assigned to the planned time point -0:15 h)
B	1	Before (-0:15 h) and 0:15 h, 0:30 h, 0:45 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 h after administration of BI 1356 and glyburide (assigned to the planned time point -0:15 h, 0:15 h, 0:30 h, 0:45 h, 1:00 h, 1:30 h, 2:00 h, 3:00 h, 4:00 h, 6:00 h, 8:00 h, and 12:00 h)
B	2, 3	In the morning at -0:15 h (Day 2) and at 0:00 h (Day 3) (assigned to the planned time point 23:45 h and 48:00 h)

Table 40: Plasma sampling schedule for glyburide (Treatment C)

Day	Time
1	Before (-0:15 h), and 0:15 h, 0:30 h, 0:45 h, 1 h, 1:30 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 h after administration of glyburide (assigned to the planned time point 0:15 h, 0:30 h, 0:45 h, 1:00 h, 1:30 h, 2:00 h, 3:00 h, 4:00 h, 6:00 h, 8:00 h, and 12:00 h)
2, 3	In the morning at -0:15 h (Day 2) and at 0:00 h (Day 3) (assigned to the planned time points 23:45 h and 48:00 h)

- **Results:** There was no significant change in linagliptin AUC and C_{max} following co-administration with glyburide (Table 41). AUC and C_{max} of glyburide were reduced by ~14% following co-administration with linagliptin, which was not clinically meaningful.

Table 41: Adjusted by-treatment geometric means and relative bioavailability of linagliptin and glyburide (in combination vs. respective controls)

Parameter	Test (N=19)	Reference (N=19)	Adjusted gMean Ratio (Test/Reference) [%]	Two-sided 90% confidence interval		Intraindividual gCV [%]
				Lower limit [%]	Upper limit [%]	
$AUC_{\tau,ss}$ [nmol·h/L]	BI + GLY	BI	101.7	97.7	105.8	7.1
$C_{max,ss}$ [nmol/L]	BI + GLY	BI	100.8	89.0	114.3	22.5
$AUC_{0-\infty}$ [ng·h/mL]	BI + GLY	GLY	85.7	79.8	92.1	12.6
C_{max} [ng/mL]	BI + GLY	GLY	86.2	79.6	93.3	14.1

- **Conclusions:**

No dose adjustments are required for linagliptin following co-administration with glyburide and vice versa for glyburide when co-administered with linagliptin.

18 Digoxin

Trial # 1218.29

Title: Relative bioavailability of digoxin after co-administration of multiple oral doses of digoxin (0.25 mg qd) and multiple oral doses of linagliptin (5 mg qd) compared to the bioavailability of multiple oral doses of digoxin (0.25 mg qd) alone in healthy male and female volunteers

- **Objective:**
  - To investigate the pharmacokinetics, safety and tolerability of digoxin with and without co-administration of BI 1356

- To evaluate the steady-state pharmacokinetics of linagliptin following co-administration with digoxin

- **Study design:**
  Open-label, randomized, two-sequence, two-period crossover design
- **Treatment groups and sample size:**
  - *Treatment Test (A)*
    Day 1-5: 0.25 mg of digoxin (Lanicor®) once daily
    Day 6-11: 0.25 mg of digoxin (Lanicor®) + 5 mg of linagliptin once daily
  - *Treatment Reference (B)*
    Day 1-11: 0.25 mg of digoxin (Lanicor®) once daily

  Washout phase between both treatments in sequence AB at least 35 days and in sequence BA at least 14 days
- **Sampling time points:**

Sampling schedule for treatments A and B are shown in Table 42 and Table 43, respectively.

Table 42: Plasma sampling schedule for linagliptin

Day	Planned time points during treatment A
1	Before (-1:00) first administration of digoxin (assigned to the planned time point -1:00 hours)
9	Before (-0:30) administration of digoxin (assigned to the planned time point 191:30 hours)
10	Before (-0:30) administration of digoxin (assigned to the planned time point 215:30 hours)
11	Before (-0:30) and 0:30, 1:00, 1:15, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 10:00 and 12:00 hours after administration of digoxin (assigned to the planned time point 239:30, 240:30, 241:00, 241:15, 241:30, 242:00, 243:00, 244:00, 246:00, 248:00, 250:00 and 252:00 hours)
12 - 17	24:00, 48:00, 72:00, 96:00, 120:00, and 144:00 hours after last administration of digoxin (day 11) (assigned to the planned time point 264:00, 288:00, 312:00, 336:00, 360:00 and 384:00 hours)

Table 43: Plasma sampling schedule for digoxin

Day	Planned time points of each treatment phase
1	Before (-1:00) first administration of digoxin (assigned to the planned time point -1:00 hours)
8	Before (-0:30) administration of digoxin (assigned to the planned time point 167:30 hours)
9	Before (-0:30) administration of digoxin (assigned to the planned time point 191:30 hours)
10	Before (-0:30) administration of digoxin (assigned to the planned time point 215:30 hours)
11	Before (-0:30) and 0:30, 1:00, 1:15, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 10:00 and 12:00 hours after administration of digoxin (assigned to the planned time point 239:30, 240:30, 241:00, 241:15, 241:30, 242:00, 243:00, 244:00, 246:00, 248:00, 250:00 and 252:00 hours)
12 - 17	24:00, 48:00, 72:00, 96:00, 120:00 and 144:00 hours after last administration of digoxin (day 11) (assigned to the planned time point 264:00, 288:00, 312:00, 336:00, 360:00 and 384:00 hours)

- **Results:** There was no significant change in digoxin AUC, C_{max}, and clearance following co-administration with linagliptin (Table 44).

Table 44: Adjusted by-treatment geometric means and relative bioavailability of digoxin

Parameter	Test (N=20)	Reference (N=20)	Adjusted gMean Ratio (Test/Reference)	Two-sided 90% confidence interval		Intra-individual gCV
Digoxin			[%]	Lower limit [%]	Upper limit [%]	[%]
$AUC_{\tau,ss}$ [ng*h/mL]	Digoxin + BI	Digoxin	101.51	96.89	106.36	8.5
Cmax,ss [ng/mL]	Digoxin + BI	Digoxin	94.21	86.62	102.46	15.4
$CL_{R,0\text{-}24,ss}$ [mL/min]	Digoxin + BI	Digoxin	99.53	91.42	108.35	15.6

- **Conclusions:**
  - Digoxin is a probe substrate for P-gp transporter
  - No dose adjustment required for substrates of P-gp following co-administration with linagliptin

19 Warfarin

Trial # 1218.28

Title: Relative bioavailability of a single oral dose of warfarin (10 mg qd) after co-administration with multiple oral doses of linagliptin (5 mg qd) compared to the bioavailability of a single oral

dose of warfarin (10 mg qd) alone in healthy male volunteers (an open label, two periods, fixed-sequence, clinical phase I study)

- **Objective:** To investigate the effect of linagliptin on pharmacokinetic and pharmacodynamic parameters of warfarin.
- **Study design:**
  Open-label, 2-period, fixed-sequence study
- **Treatment groups and sample size:**
  - *Reference Treatment A*:
    10 mg warfarin tablet
  - *Test Treatment B*:
    5 mg linagliptin with a single oral dose of 10 mg warfarin (i.e. Day 1 of Visit 4)

  These two treatment periods were separated by washout period of at least 14 days.
- **Sampling time points:**
  - **PK**
    Warfarin (Period 1 and 2)
    Baseline, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and168 hr
  - **PD**
    PT and INR (Period 1 and 2)
    Baseline, 6, 12, 24, 36, 48, and 168 hr
- **Results:** There was no significant difference in PK of R-warfarin and S-warfarin following co-administration with linagliptin as shown in Table 45 and Table 46, respectively. Linagliptin also did not affect the PD endpoints of warfarin (Table 47 and Figure 16). For comparison of PD endpoints (INR and PT) with and without linagliptin, the upper limits of geometric means on E_{max} of INR and PT were higher than 125%, which was likely because of high variability in these endpoints (geometric CV% of 35.9% and 35.5%, Table 47).

Table 45: Adjusted by-treatment, geometric mean and relative bioavailability of R-warfarin

Parameter	Test	Reference	Adjusted gMean Ratio (Test/Reference) [%]	Two-sided 90% confidence interval		Intra-individual gCV [%]
				Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [ng·h/mL]	BI + Warfarin	Warfarin	98.54	95.67	101.49	5.1
C_{max} [ng/mL]	BI + Warfarin	Warfarin	99.66	94.66	104.93	8.9

Table 46: Adjusted by-treatment, geometric mean and relative bioavailability of S-warfarin

Parameter	Test	Reference	Adjusted gMean Ratio (Test/Reference) [%]	Two-sided 90% confidence interval		Intra-individual gCV [%]
				Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [ng·h/mL]	BI + Warfarin	Warfarin	102.98	99.08	107.03	6.7
C_{max} [ng/mL]	BI + Warfarin	Warfarin	100.86	93.70	108.56	12.8

Table 47: Adjusted by treatment geometric mean for INR and PT

Parameter	Test	Reference	Adjusted gMean Ratio (Test/Reference) [%]	Two-sided 90% confidence interval		Intra-individual gCV [%]
				Lower limit [%]	Upper limit [%]	
INR						
AUC_{0-168}	BI + Warfarin	Warfarin	93.35	86.20	101.08	13.8
E_{max}	BI + Warfarin	Warfarin	104.27	85.22	127.59	35.9
PT						
AUC_{0-168} [s h]	BI + Warfarin	Warfarin	103.17	95.36	111.61	13.6
E_{max} [s]	BI + Warfarin	Warfarin	115.12	94.27	140.59	35.5

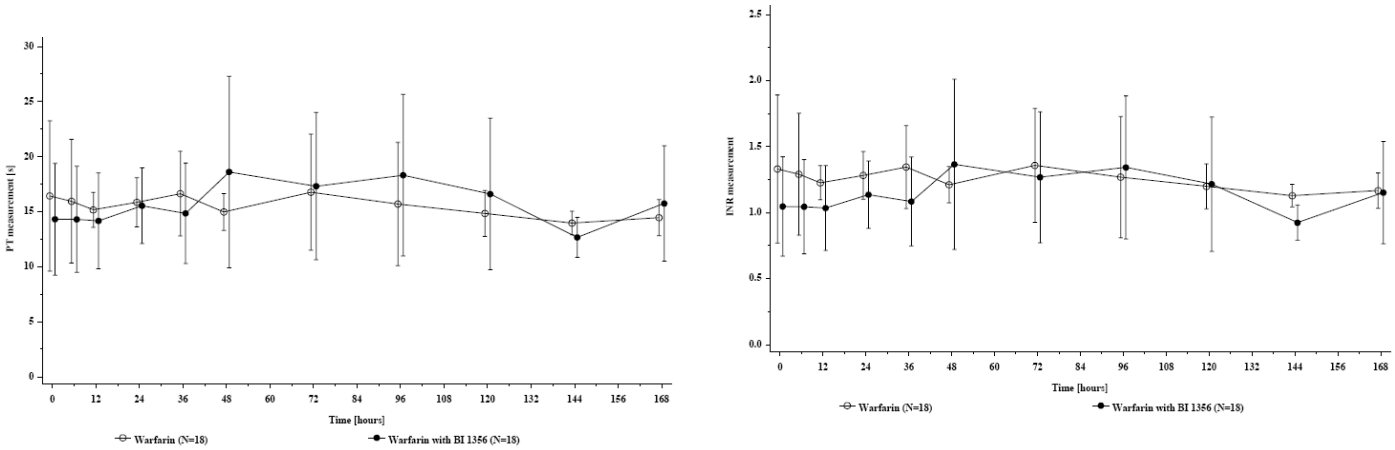


Figure 16: Time-profiles of PT (left panel) and INR (right panel) (arithmetic mean, SD) after oral administration of 10 mg warfarin alone or in combination with 5 mg linagliptin

- **Conclusions:**
  - Warfarin is a probe substrate for CYP 2C9 enzyme.
  - No dose adjustment required for substrates of CYP 2C9 following co-administration with linagliptin

20 Oral Contraceptives

Trial # 1218.44

Title: An open, two-period, fixed-sequence, phase I trial to evaluate the effect of multiple doses of linagliptin on the multiple-dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel

- **Objective:**
  To investigate the effect of multiple oral doses of 5 mg linagliptin on the steady-state pharmacokinetics of ethinylestradiol (EE) and levonorgestrel (LNG), the components of Microgynon
- **Study design:**
  Open-label, 2-period, fixed-sequence
- **Test drug:**
  - Linagliptin – 5 mg once daily

- Microgynon® - 30 µg EE + 150 µg LNG once daily

- **Treatment groups and sample size:**
  - *Reference treatment:*
    Microgynon® once daily for 14 days
  - *Test treatment:*
    Microgynon® once daily + linagliptin 5 mg once daily from day 15 to 21
- **Sampling time points:**
  For analysis of EE and LNG:
  (For reference) Shortly before drug administration on days 5, 10, 11, 12, 13, and over a time period of 24 hrs on day 14 and (for Test) on days 18, 19, 20, and over a time period of 24 hrs on day 21
- **Results:** The geometric mean ratio (90% CI) for $C_{max,ss}$ and $AUC_{\tau,ss}$ of ethinylestradiol and levonorgestrel were within 80-125% range, indicating no clinically relevant effect of linagliptin co-administration on PK of oral contraceptives.

Table 48: Adjusted by-treatment geometric means and relative bioavailability of ethinylestradiol and levonorgestrel

Parameter	Test (N=18)	Reference (N=18)	Adjusted gMean ratio (T/R)	Two-sided 90% confidence interval		Intra-individual gCV
				Lower limit	Upper limit	
			[%]	[%]	[%]	[%]
Ethinylestradiol						
$AUC_{\tau,ss}$ [pg·h/mL]	BI 1356 + Microgynon	Microgynon	101.4	97.24	105.79	7.3
$C_{max,ss}$ [pg/mL]	BI 1356 + Microgynon	Microgynon	107.8	99.71	116.63	13.6
Levonorgestrel						
$AUC_{\tau,ss}$ [ng·h/mL]	BI 1356 + Microgynon	Microgynon	108.8	104.52	113.34	7.0
$C_{max,ss}$ [ng/mL]	BI 1356 + Microgynon	Microgynon	113.5	106.08	121.32	11.6

- **Conclusions:**
  No need to change the dosing schedule of oral contraceptives when co-administered with linagliptin

21 Simvastatin

Trial # 1218.9

Title: The effect of multiple oral doses of linagliptin as tablets once daily for six days on the pharmacokinetics, safety and tolerability of multiple oral doses of 40 mg simvastatin given once daily for 20 days and on the pharmacokinetics of its metabolite simvastatin acid. An open-label study in healthy male volunteers

- **Objective:**

To investigate the multiple dose pharmacokinetics, safety and tolerability of simvastatin and simvastatin acid with and without concomitant administration of linagliptin

- **Study design:**
  Open-label, multiple dose design, partly in-house study
- **Treatment groups and sample size:**
  - Simvastatin 40 mg once-daily days 1-6 followed by co-administration with 10 mg linagliptin for 6 days (days 7-12), which was further followed by administration of simvastatin alone for 8 days (days 13-20).
  - Number of subjects treated - 20
- **Results:**
  The mean AUC for simvastatin increased by 33-34%, while the AUC of simvastatin acid increased by 24-33% following co-administration with linagliptin (Table 49). The C_{max} of simvastatin and simvastatin acid also increased by 10-21% (Table 49).

Table 49: Adjusted by-treatment geometric means and relative bioavailability for simvastatin and simvastatin acid

Parameter	Test (N=20)	Reference (N=20)	Intra-indiv. gCV	Adjusted gMean Ratio (Test/Reference)	Two sided 90% Confidence Interval	
			[%]	[%]	Lower limit [%]	Upper limit [%]
Simvastatin						
$AUC_{\tau,ss}$ [ng·h/mL]	Simvast.+BI1356 (D12)	Simvastatin (D6)	21.5	134.2	119.4	150.7
$AUC_{0-12,ss}$ [ng·h/mL]	Simvast.+BI1356 (D12)	Simvastatin (D6)	17.9	132.5	120.2	146.1
$C_{max,ss}$ [ng/mL]	Simvast.+BI1356 (D12)	Simvastatin (D6)	39.7	110.0	89.3	135.6
Simvastatin acid						
$AUC_{\tau,ss}$ [ng·h/mL]	Simvast.+BI1356 (D12)	Simvastatin (D6)	22.3	133.3	118.1	150.3
$AUC_{0-12,ss}$ [ng·h/mL]	Simvast.+BI1356 (D12)	Simvastatin (D6)	26.8	123.7	107.1	142.9
$C_{max,ss}$ [ng/mL]	Simvast.+BI1356 (D12)	Simvastatin (D6)	32.6	120.7	101.5	143.6

- **Conclusions:**
  - Simvastatin is a probe substrate of CYP 3A4
  - Minor increase in AUC and C_{max} of simvastatin and simvastatin acid indicates weak inhibition of CYP 3A4 by multiple dosing with 10 mg linagliptin
  - No dose adjustment required for simvastatin following co-administration with linagliptin

BIOPHARMACEUTICS

22 Food Effect (10 mg)

Trial # 1218.8

Title: Relative bioavailability of 1 mg and 10 mg linagliptin as powder in the bottle (PIB) reconstituted with 0.1% tartaric acid compared to 1 mg and 10 mg linagliptin as tablets as single oral administration in healthy male volunteers (separately at each dose level) including the influence of food (standardized high fat breakfast) on the bioavailability of 10 mg linagliptin as tablet in a single dose, open-label, randomized, two-way (1 mg) and three-way (10 mg) crossover trial.

- **Objective:**
  - To investigate the relative bioavailability of 1 mg and 10 mg linagliptin as PIB reconstituted with 0.1% tartaric acid vs. 1 mg and 10 mg linagliptin as tablet
  - To investigate the effect of food for the 10 mg tablet dose group
- **Study design:**
  With respect to assessment of food effect:
  - Linagliptin 10 mg dose was administered after a standardized high fat breakfast or in fasting state.
  - Composition of high-fat breakfast was in agreement with FDA recommendations and included 2 eggs (120 g), 2 strips of bacon (30 g), butter (30 g), 2 toast bread slices (60 g), hash brown potatoes (120 g), and whole milk (240 mL) – with a total calories of 945 kcal or 3969 kJ.
- **Results:** Co-administration with food reduced C_{max} by 25% but had no considerable effect on AUC. Linagliptin is used for chronic treatment; therefore, decrease in C_{max} is not considered clinically relevant.

Parameter	N	Test	Reference	Intra-indiv. gCV (%)	Adjusted gMean Ratio (Test/Reference) (%)	Two sided 90 % Confidence Interval	
						Lower limit [%]	Upper limit [%]
C_{max} [ng/mL]	12	10 mg tablet with food	10 mg tablet	30.8	75.08	60.742	92.792
$AUC_{0-\infty}$ [ng·h/mL]	12	10 mg tablet with food	10 mg tablet	8.4	95.77	90.265	101.618

- **Conclusions:** Linagliptin can be taken with and without food.

23 Food Effect (5 mg)

Trial # 1218.34

Title: Relative bioavailability of a 5 mg linagliptin tablet administered with and without food to healthy male and female subjects in an open, randomized, single-dose, two-way crossover, phase I trial

- **Objective:** To investigate the food effect on the relative bioavailability and pharmacokinetics of a 5 mg linagliptin
- **Study design:**
  - Open-label, randomized, single-dose, two-way crossover design
  - 5 mg dose was administered after a high-fat breakfast or in fasted state. High-fat breakfast composition was same as mentioned under study 1218.8.
- **Results:**
  Co-administration with food had no effect on extent of absorption (AUC) but C_{max} was reduced by about 14%. This reduction in C_{max} is not considered clinically relevant.

Table 50: Comparison and 90% confidence intervals of the PK parameters for linagliptin administered with and without food

Parameter	N	Test	Reference	Intra-individual gCV (%)	Adjusted gMean ratio (Test/Reference) (%)	Two-sided 90% confidence interval	
						Lower limit [%]	Upper limit [%]
AUC_{0-72} [nmol·h/L]	32/31	fed	fasted	12.4	103.5	98.1	109.2
C_{max} [nmol/L]	32/31	fed	fasted	26.1	84.7	75.9	94.6

- **Conclusions:** Linagliptin can be administered with and without food.

24 BA Comparison Of Test Formulations

Trial # 1218.25

Title: Bioavailability of linagliptin after single oral administration of 5 mg linagliptin given as tablet formulation TF IIb relative to tablet formulation TF II and tablet formulation iFF in healthy male volunteers

- **Objective:**
  To investigate the relative bioavailability of 5 mg linagliptin as tablet formulations TF II and iFF vs. 5 mg linagliptin as tablet TF IIb.
- **Study design:**
  Open-label, randomized, three-way crossover design with sample size.
- **Formulations compared:**
  - TF II – trial formulation 2, used in early clinical trials
  - TF IIb – TF II optimized for stability
  - iFF – intended final formulation (b) (4)
- **Results:**

At the proposed to-be-marketed dose of 5 mg, all three formulations were bioequivalent (Table 51).

Table 51: Comparison and 90% confidence intervals of the pharmacokinetic parameters between the different formulations based on the treated set (N=24)

Parameter	N	Test	Reference	Intra-indiv. gCV (%)	Adjusted gMean Ratio (Test/Reference) (%)	Two-sided 90% Confidence Interval	
						Lower limit [%]	Upper limit [%]
AUC_{0-24} [nmol·h/L]	24	iFF	TF IIb	14.9	96.6	89.9	103.8
C_{max} [nmol/L]	24	iFF	TF IIb	29.7	102.7	89.2	118.2
$AUC_{0-\infty}$ [nmol·h/L]	24	iFF	TF IIb	13.6	96.4	90.2	102.9
AUC_{0-24} [nmol·h/L]	24	TF II	TF IIb	14.9	98.5	91.7	105.9
C_{max} [nmol/L]	24	TF II	TF IIb	29.7	101.2	87.9	116.5
$AUC_{0-\infty}$ [nmol·h/L]	24	TF II	TF IIb	13.6	99.0	92.7	105.8

DOSE RESPONSE TRIALS

25 Phase 2 Dose Ranging Trial

Trial # 1218.5

Title: A randomized, double-blind, placebo-controlled, five parallel group study investigating the efficacy and safety of linagliptin (0.5 mg, 2.5 mg and 5 mg administered orally once daily) over 12 weeks in drug naïve and treated patients with Type 2 diabetes with insufficient glycemic control

- **Objective:**
  To investigate the efficacy of linagliptin versus placebo, and investigation of safety and population pharmacokinetics
- **Study design:**
  Randomized, double-blind, placebo-controlled, open-label metformin, parallel group comparison
- **Treatment groups and sample size:**
  - Placebo, N=63
  - Linagliptin 0.5 mg, N=57
  - Linagliptin 2.5 mg, N=55
  - Linagliptin 5 mg, N=54
  - Metformin 500 mg bid for 4 weeks then 1000 mg bid for 8 weeks, N=65
- **Results:**
  The mean change from baseline and placebo adjusted change from baseline in HbA1c at week 12th for linagliptin treatment are shown in Table 52. The change of HbA1c from baseline at Week 12 was statistically significant, for linagliptin 2.5 mg and linagliptin 5 mg when compared to placebo. The slight decrease in HbA1c of -0.14%, which was observed in the patients who were treated with the linagliptin 0.5 mg dose, was not statistically significant (p-value: 0.327). The changes in HbA1c across time are shown in Figure 17. Most of the HbA1c

lowering effect of linagliptin occurred between baseline and week 8, with minimal change between week 8 and week 12 (Figure 17).

Table 52: Comparison of treatments for change of HbA1c from baseline at week 12 (Full Analysis Set)

	Placebo	BI 1356 0.5mg	BI 1356 2.5 mg	BI 1356 5 mg
Number of patients	63	57	55	54
HbA1C [%]				
Adjusted Mean (SE)	0.18 (.10)	0.04 (.10)	-0.24 (.10)	-0.28 (.10)
HbA1C difference to Placebo [%]				
Adjusted Mean (SE)		-0.14 (.14)	-0.42 (.14)	-0.46 (.14)
95% CI		(-0.41, 0.14)	(-0.69, -0.14)	(-0.74, -0.18)
P-value		0.3271	0.0032	0.0012

Note: The above results are based on analysis that includes BI 1356 doses, Metformin and Placebo data

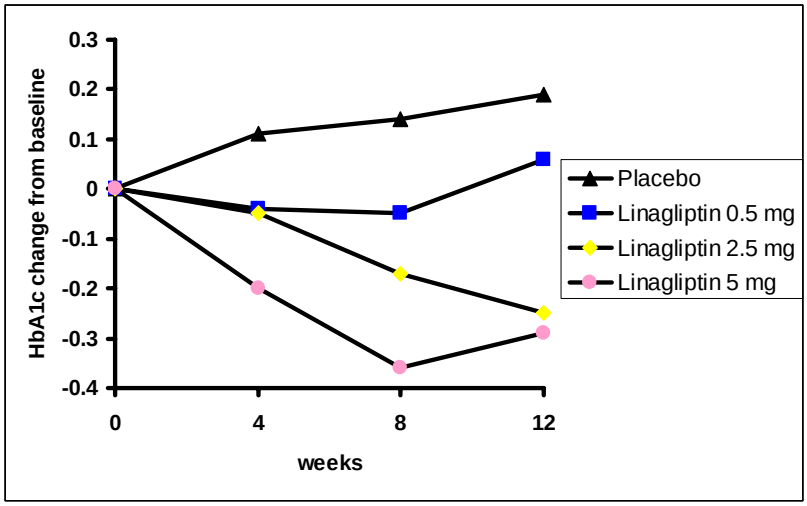


Figure 17: Adjusted mean values of plasma HbA1c at baseline, 4, 8, and 12 weeks after oral administration of linagliptin or metformin or placebo in a 12 week study 1218.5

- **Conclusions:** Linagliptin 5 mg dose provides maximum benefit with respect to reduction in HbA1c from baseline at week 12

26 Phase 2 Dose Ranging Trial

Trial # 1218.6

Title: A randomized, double-blind, placebo-controlled, five parallel groups study investigating the efficacy and safety of linagliptin (1 mg, 5 mg and 10 mg administered orally once daily) over 12 weeks as add-on therapy in patients with type 2 diabetes and insufficient glycaemic control despite metformin therapy, including an open-label glimepiride treatment arm

- **Objective:**
  - To investigate the efficacy, safety, and tolerability of linagliptin versus placebo
  - To explore the efficacy of glimepiride treatment vs. placebo for sensitivity analysis
  - To investigate the population pharmacokinetics
- **Study design:**
  Randomized, double-blind, placebo-controlled, open-label glimepiride, parallel group comparison
- **Treatment groups and sample size:**
  Following treatments were administered as an add-on therapy to metformin
  - Placebo, N=71
  - Linagliptin 1 mg once daily, N=65
  - Linagliptin 5 mg once daily, N=66
  - Linagliptin 10 mg once daily, N=66
  - Glimepiride 1 mg to 3 mg once daily, N=65

- **Results:**
  The mean change from baseline and placebo adjusted change from baseline in HbA1c at week 12th for linagliptin administration with metformin are shown in Table 53. For each of the linagliptin treatments, the change in HbA1c from baseline to week 12 was superior to placebo. The effect size was similar between linagliptin 5 mg and 10 mg dose. The changes in HbA1c across time are shown in Figure 18. Similar to trial 1218.5, most of the HbA1c lowering effect of linagliptin occurred between baseline and week 8. More than 80% patients on 5 mg and 10 mg dose had DPP-4 inhibition of ≥ 80% (Table 54).

Table 53: Adjusted means for HbA1c change from baseline at week 12 (Full Analysis Set)

HbA1c (%)	Placebo	BI 1356 1 mg	BI 1356 5 mg	BI 1356 10 mg
Number of patients	70	64	62	66
Adjusted mean change from baseline (SE)	0.25 (0.10)	–0.15 (0.10)	–0.48 (0.11)	–0.42 (0.10)
Difference to placebo (SE) 95% CI p-value		–0.40 (0.14) (–0.68, –0.12) 0.0055	–0.73 (0.14) (–1.01, –0.44) <.0001	–0.67 (0.14) (–0.95, –0.39) <.0001

Means are adjusted based on a model with baseline HbA1c, treatment

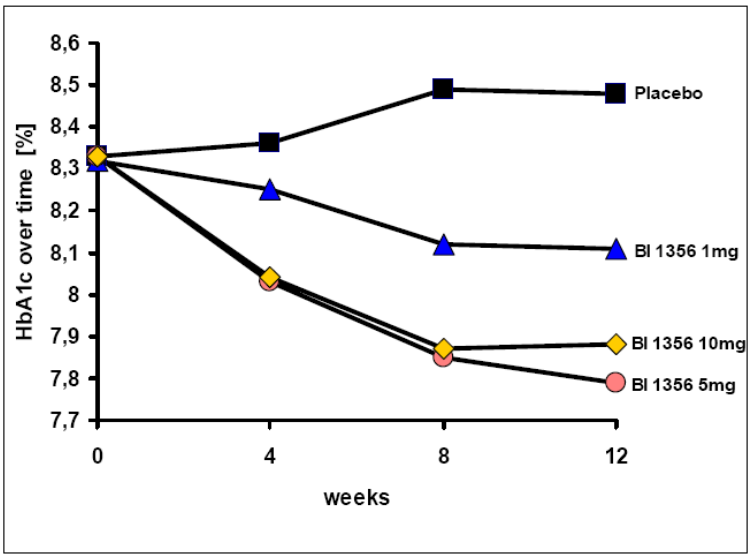


Figure 18: Adjusted mean values of plasma HbA1c at baseline, 4, 8, and 12 weeks after oral administration of linagliptin (BI 1356) or placebo in combination with metformin in a 12 week study 1218.6

Table 54: DPP-4 inhibition (median and 20% percentile) and frequency of patients with trough DPP-4 inhibition of 80% or above at week 12

	Placebo	BI 1356 1 mg	BI 1356 5 mg	BI 1356 10 mg
Number of patients	71	65	66	66
Number of patients with DPP-4 data	53	53	54	61
20% percentile of DPP-4 inhibition	−15%	47%	80%	87%
Median of DPP-4 inhibition	1%	62%	85%	89%
Frequency of patients with DPP-4 inhibition of ≥80% at trough	0%	8%	87%	93%

- **Conclusions:**
  - There appears to be no added benefit by increasing the dose from 5 mg to 10 mg with respect to HbA1c reduction.
  - Overall based on results from trials 1218.5 and 1218.6, the reduction in HbA1c appears to reach maximum at dose between 2.5 mg and 5 mg, and there appears to be no added benefit of increasing the dose from 5 mg to 10 mg.

OTHERS

Summary of extent of DPP-4 inhibition from all trials in which DPP-4 inhibition was evaluated (Table 55).

Table 55: Trough median (range) DPP-4 inhibition after multiple dosing of linagliptin (1 mg, 2.5 mg, 5 mg and 10 mg) to patients and healthy volunteers

	1 mg	2.5 mg	5 mg	10 mg
	Patients	Patients	Patients	Patients
Caucasians	Median (range)	Median (range)	Median (range)	Median (range)
1218.2 (2 week MRD in T2DM patients)	60.0 (57.0 - 71.0)	77.0 (73.0 - 82.0)	85.5 (78.0 – 88.0)	90.0 (85.0 – 92.0)
1218.3 (4 week MRD in T2DM patients)		81.0 (68.0 – 90.0)	88.0 (81.0 – 92.0)	90.0 (87.0 – 93.0)
1218.4 (DDI metformin in HV) (linagliptin alone)				91.0 (86.0 – 93.0)
1218.4 (DDI metformin in HV) (linagliptin plus metformin)				92.5 (89.0 – 94.0)
1218.67 (DDI rifampicin in HV) (linagliptin alone)			81.1 (59.6 – 88.1)	
1218.67 (DDI rifampicin in HV) (linagliptin plus rifampicin)			52.7 (37.2 – 69.9)	
1218.26 (RI study) (mild RI)*			87.2 (85.8 – 90.0)	
1218.26 (RI study) (moderate RI)*			91.1 (89.0 – 92.9)	
1218.26 (RI study) (T2DM patients with severe RI)			90.6 (86.0 – 94.2)	
1218.26 (RI study) (control group HV)			84.0 (70.3 – 88.3)	
1218.26 (RI study) (control group T2DM patients)			89.4 (84.8 – 92.5)	
1218.27 (HI study) (mild HI)*			90.4 (83.0 – 92.8)	
1218.27 (HI study) (moderate HI)*			88.7 (71.2 – 93.6)	
1218.27 (HI study) (control group HV)			90.6 (85.5 – 93.8)	
1218.37 (4 week mechanistic study in T2DM patients)			82.2 (77.1 – 91.7)	
Japanese				
1218.11 (SRD and 2 week MRD in healthy volunteers)		78.0 (75.0 – 85.0)	86.0 (81.0 – 89.0)	90.0 (87.0 – 91.0)
1218.12 (4 week MRD in T2DM patients)		80.0 (67.0 – 85.0)		90.0 (86.0 – 92.0)
Pooled analysis from studies 1218.2, 1218.3, 1218.5 and 1218.6 (PopPKPD)	60.0	77.0	84.8	89.5

* impaired patients without T2DM
RI renal impairment
HI hepatic impairment
HV healthy volunteers
PopPKPD population pharmacokinetic/pharmacodynamic analysis

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

/s/

LOKESH JAIN
03/07/2011

SALLY Y CHOE
03/08/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-280 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DMEP		
Sponsor:	Boehringer Ingelheim	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Linagliptin Film-coated IR Tablets	**Date Assigned:**	Jul 8, 2010
Indication:	Type 2 diabetes mellitus	**Date of Review:**	Feb 21, 2011
Formulation/strengths	IR Tablets, 5 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
July 2, 2010	July 7, 2010	Jul 8, 2010	May 2011
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications/Role of dissolution on QbD		

REVIEW SUMMARY:

The sponsor has developed a formulation for linagliptin (an inhibitor of plasma dipeptidyl peptidase 4 activity) consisting of an immediate release (IR) film-coated tablet for the once daily treatment of type 2 diabetes mellitus. Linagliptin IR tablets will be marketed in the United States as 5mg IR Tablets. Linagliptin IR Tablet formulation used in the pivotal phase III clinical efficacy trial and safety trials is similar to the to-be-marketed formulation.

The dissolution method and specifications being proposed by the sponsor for linagliptin IR tablets based on the in vitro performance of BA/BE batches, clinical batches, and stability batches are as follows:

Drug Name	**Dosage Form**	**USP Apparatus**	**Speed (rpm)**	**Medium**	**Volume (mL)**	**Acceptance criteria**
Linagliptin	IR Tablet	I (Basket)	50	01N HCl	900, 37 °C ± 0.5 °C	Q=(b) (4) at 30 min

The comparability of data obtained with three of the formulations used through out the development of the product (namely, TF-II, TF-IIb and iFF) was demonstrated in a relative bioavailability study, despite the differences observed in the in vitro dissolution (F_2 < 50) between these formulations. Under these circumstances, the dissolution method may be considered over-discriminating. Because dissolution specification was set by this reviewer based on the slowest profile of the batches tested in the BE study, it was possible to widen this specification (b) (4) making the specification clinically relevant with lower probability of rejecting batches that are bioequivalent. Therefore, the dissolution method is considered highly sensitive to CMC changes.

(b) (4)

(b) (4)

The final to-be-marketed formulation (FF) and the formulation used in the clinical trials (iFF) differed (b) (4) according to FDA Guidance for Industry: Scale-up and post-approval changes (SUPAC-IR) and does not require a dissolution profile comparison or BE testing.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 201-280 (000) submitted on July 2, 2010. We found this NDA acceptable from the biopharmaceutics perspective.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

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

cc: ADorantes, RChiang, STran, ShMarkofsky, LJain, RChiang, Khushboo, OStephens

INTRODUCTION
The sponsor has developed a formulation for linagliptin (an inhibitor of plasma dipeptidyl peptidase 4 activity) consisting of an immediate release (IR) film-coated tablet for the once daily treatment of type 2 diabetes mellitus. Linagliptin IR tablets will be marketed in the United States as 5mg IR Tablets. Linagliptin IR Tablet formulation used in the pivotal phase III clinical efficacy trial and safety trials is similar to the to-be-marketed formulation.

(b) (4)

11 Pages have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

---

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

/s/

SANDRA SUAREZ
02/28/2011

PATRICK J MARROUM
03/01/2011

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**201280**	**Brand Name**	**Ondero**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Linagliptin**
Medical Division	**Metabolic and Endocrine Products**	**Drug Class**	**DPP-4 inhibitor**
OCP Reviewer	**Lokesh Jain, Ph.D.**	**Indication(s)**	**Type 2 diabetes**
OCP Team Leader	**Sally Choe, Ph.D.**	**Dosage Form**	**Tablets**
Pharmacometrics Reviewer	**Lokesh Jain, Ph.D. & Justin C. Earp, Ph.D.**	**Dosing Regimen**	**5 mg QD**
Date of Submission	**07/02/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**03/07/2011**	**Sponsor**	**Boehringer Ingelheim Pharmaceuticals, Inc.**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**02/05/2011**		

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**	23		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		1218.7
Isozyme characterization:	**X**	**3**		in vitro
Blood/plasma ratio:	**X**	**1**		1218.7 (same as mass balance)
Plasma protein binding:	**X**	**9**		includes studies to assess the dose dependent binding to DPP-4 and tissue distribution
Transporter specificity:	**X**	**2**		U05-1795 Module 4.2.2.2 U06-3019 Module 4.2.2.3
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		1218.1
multiple dose:	**X**	**2**		1218.11, 1218.58
Patients-				
single dose:	**X**			
multiple dose:	**X**	**4**		1218.2, 1218.3, 1218.12, 1218.26
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	**X**	**1**		1218.33
Drug-drug interaction studies -				

In-vivo effects on primary drug:	**X**	**5**		3 of these studies [i.e., 1218..4, 1218.13, 1218.30] are also part of 'in-vivo effects of primary drug'
In-vivo effects of primary drug:	**X**	**7**		3 of these 7 studies also looked at in vivo effects on primary drug
In-vitro:	**X**	**3**		U05-2525 Module 4.2.2.4 U04-2193 Module 4.2.2.4 U08-1198 Module 5.3.2.2
Subpopulation studies -				
ethnicity:	**X**	**3**		Japanese [1218.11, 1218.12] & Chinese [1218.1218.58]
gender:				
pediatrics:				Requested waiver for age ≤ 9 years and deferral for ages 10-(b)(4) years
geriatrics:				
renal impairment:	**X**	**1**		Phase 1 trial in T2DM and non-diabetic subjects with different degree of renal impairment
hepatic impairment:	**X**	**1**		Phase 1 trial in patients with different degree of hepatic impairment
PD -				
Phase 2:	**X**	**4**		1218.5, 1218.6, 1218.12, 1218.37
Phase 3:	**X**	**9**		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**2**		Population PK and PK-PD analysis with both rich & sparse data Phase 1 trials: 1218.2, 1218.3 Phase 2 trials: 1218. 5, 1218.6
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		1218.10
Relative bioavailability -				
solution as reference:	**X**	**1**		1218.8
alternate formulation as reference:	**X**	**1**		1218.25
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		1218.8 & 1218.34
Bio-waiver request based on BCS				
BCS class	**X**			
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	**X**	**1**		Thorough QTc study
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Not submitted
Literature References				
Total Number of Studies		**82**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	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	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Dose was selected based on results of trials 1218.5, 1218.6, & 1218.23
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			A PK-PD model was developed between linagliptin plasma concentration and DPP-4 activity
14	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		Sponsor states large safety margin for this drug and recommends no dose adjustments based on intrinsic and extrinsic factors. At this stage it is not clear whether sponsor used the exposure-response analysis to support these recommendations or not.
15	Are the pediatric exclusivity studies adequately designed to demonstrate			X	

	effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		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.
- None

Lokesh Jain	08/02/10
Reviewing Clinical Pharmacologist	Date
Sally Choe	08/02/10
Team Leader/Supervisor	Date

Submission in brief:

Indication and mechanism of action

The Boehringer Ingelheim Pharmaceuticals, Inc. has submitted the NDA 201280 to seek the marketing approval for Linagliptin (Ondero®) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The recommended dose is 5 mg once daily (qd).

Linagliptin is an orally administered dipeptidyl peptidase-4 (DPP-4) inhibitor. The inhibition of DPP-4 prolongs the half-life of endogenous incretin hormones, GLP-1 (glucagon-like peptide 1) and GIP (glucose dependent insulinotropic polypeptide). Both incretin hormones are involved in physiological regulation of glucose homeostasis. They stimulate the release of insulin and lower the plasma glucagon levels. GLP-1 activity ceases when the glucose concentration falls below 55 mg/dL, suggesting that prolongation of the half-life of GLP-1 by DPP-4 inhibitors bears little risk of hypoglycaemia. Sponsor reported Linagliptin's IC_{50} for DPP-4 inhibition is 1 nM.

Based on sponsor's recommendation, unique feature of this molecule compared to previous DPP-4 inhibitors (i.e., Saxagliptin, Sitagliptin, and Vildagliptin) is that it can be administered to renally impaired patients without dose adjustments.

Summary of information submitted

The NDA 201280 consists of 24 Phase 1 studies, 4 Phase 2 studies, and 9 Phase 3 studies. The clinical pharmacology information for Linagliptin is mainly derived from Phase 1 studies as well as non-clinical studies evaluating permeability, plasma protein binding, role of transporters, and potential for CYP 450 metabolic enzymes inhibition and induction. Population pharmacokinetics analysis was performed to assess the effect of covariates. Population pharmacokinetics-pharmacodynamics analysis was also performed to analyze the exposure-response relationship. In addition, 21 bioanalytical reports have been submitted to measure the levels of parent compound, main metabolite CD1750, and PK/PD markers such as C-peptide, insulin, HbA1c, glucose, and 1,5 anhydroglucitol.

Rational for 5 mg qd dose selection

The 5 mg qd dose was selected based on results of 2 dose ranging Phase 2 studies in T2DM patients of 12 weeks duration (Study ID: 1218.5 and 1218.6), and one Phase 3 study comparing the 5 mg and 10 mg dose in Japanese patients (Study ID: 1218.23). These studies compared the effect of linagliptin on efficacy biomarkers DPP-4, HbA1c, and fasting plasma glucose (FPG) across doses ranging from 0.5 to 10 mg. Study 1218.5 compared linagliptin doses of 0.5 mg, 2.5 mg, and 5 mg qd, while study 1218.6 compared 1 mg, 5 mg, and 10 mg qd.

The results from these trials are summarized in **Table 1**. More than 80% inhibition of DPP-4 was only achieved with doses of 5 mg or 10 mg, therefore, only these two doses were considered further. Going from 5 mg to 10 mg did not substantially improve the change in HbA1c and FPG from placebo/baseline. Based on that final dose was chosen as 5 mg.

Sponsor reported that no dose-dependent increase in adverse events was observed in these trials. Sponsor stated that it was consistent with the Phase 1 data where single doses of up to 600 mg were taken without any safety concerns. Hence, sponsor based the selection of dose entirely on efficacy considerations.

Table 1: Results from trials used to support the selection of final 5 mg dose.

Parameter	1218.5			1218.6			1218.23	
	0.5 mg	2.5 mg	5 mg	1 mg	5 mg	10 mg	5 mg	10 mg
DPP-4 inhibition (%)	38.5	74.5	81.0	63.0	85.0	90.0	81.5	88.0
HbA1c								
Change from baseline (%)	0.04	-0.24	-0.28	-0.16	-0.48	-0.42	-0.24	-0.25
Placebo-corrected change (%)	-0.14	-0.41	-0.46	-0.40	-0.72	-0.67	-0.87	-0.88
FPG								
Change from baseline (mg/dL)	7.89	-16.14	-9.92	-6.40	-22.12	-16.26	-12.46	-12.86
Placebo-corrected change (mg/dL)	2.44	-21.59	-15.37	-19.02	-34.74	-28.88	-19.99	-20.39

Efficacy in Phase 3 trials

The Phase 3 studies supporting the efficacy of linagliptin in T2DM patients included:

- Pivotal double-blind placebo controlled studies with a duration of treatment of 24 weeks (studies 1218.15, 1218.16, 1218.17, and 1218.18)

- A double-blind active-controlled trial (study 1218.20)
- Double-blind placebo-controlled trials of 18 weeks duration (studies 1218.35 and 1218.50)
- Placebo- and active-controlled study of 52 weeks with an extension for safety evaluation (study 1218.23)
- An open-label extension study (study 1218.40)

These Phase 3 studies compared the efficacy of linagliptin arm with placebo arm, when these were given alone or in combination with metformin/pioglitazone/metformin+sulphonyl urea.

Results of these studies are summarized in **Table 2**. Except study 1218.20, others show a significant difference in decrease in HbA1c following addition of linagliptin to therapy compared to placebo or active comparator. Similar differences were observed in levels of FPG between two treatment groups.

Table 2. Summary of results for Phase 3 trials

Study	**Treatment Arm**	**Change from baseline in HbA1c**		**Difference from placebo/active control**		
		Mean (SD)	**Adjusted mean (SE)**	**Adjusted mean (SE)**	**95% CI**	**p-value**
1218.15	Placebo	-0.75 (1.21)	-0.56 (0.09)			
	Linagliptin	-1.25 (1.07)	-1.07 (0.06)	-0.51 (0.10)	(-0.71, -0.30)	<0.0001
1218.16	Placebo	0.22 (1.07)	0.25 (0.07)			
	Linagliptin	-0.46 (0.81)	-0.44 (0.05)	-0.69 (0.08)	(-0.85, -0.53)	<0.0001
1218.17	Placebo	0.10 (1.00)	0.15 (0.06)			
	Linagliptin	-0.56 (0.83)	-0.49 (0.04)	-0.64 (0.07)	(-0.78, -0.50)	<0.0001
1218.18	Placebo	-0.10 (0.87)	-0.10 (0.05)			
	Linagliptin	-0.72 (0.86)	-0.72 (0.03)	-0.62 (0.06)	(-0.73, -0.50)	<0.0001
1218.20	Glimepiride	-0.65 (0.88)	-0.60 (0.03)			
	Linagliptin	-0.43 (0.82)	-0.38 (0.03)	0.22 (0.04)	(0.13, 0.31)[a]	0.0007[b]
1218.35	Placebo	-0.11 (0.76)	-0.07 (0.10)			
	Linagliptin	-0.58 (0.91)	-0.54 (0.07)	-0.47 (0.12)	(-0.70, -0.24)	<0.0001
1218.50	Placebo	0.25 (1.06)	0.06 (0.22)			
	Linagliptin	-0.33 (1.03)	-0.49 (0.21)	-0.55 (0.14)	(-0.83, -0.27)	0.0001
1218.23	Voglibose	-0.10 (0.99)	0.19 (0.08)			
	Linagliptin	-0.44 (0.86)	-0.13 (0.08)	-0.32 (0.09)	(-0.51, -0.14)	0.0006

a. 97.5% CI
b. Non-inferiority test (non-inferiority margin: 0.35%)

Effect of intrinsic/extrinsic factors on dose

The 5 mg once daily (qd) dose is being proposed regardless of food. No dose adjustments have been proposed based on studied intrinsic and extrinsic factors such as age, gender, race, renal function, hepatic function, and co-administration with metformin, pioglitazone, ritonavir, rifampicin, glyburide, warfarin, digoxin, simvastatin and ethinylestradiol. Sponsor notes that linagliptin has a large safety window and no dose adjustments would be needed even with 2- and 3-folds increase in AUC and C_{max}, respectively, following co-administration with ritonavir.

To-be-marketed formulation vs. clinical development formulation

The intended final formulation (iFF) was used in all Phase 3 efficacy and safety clinical studies, as well as in some Phase 1 and Phase 2 clinical studies. The final to-be-marketed formulation (FF) differs from the iFF in following 2 aspects:

(b) (4)

Sponsor claims that these minor differences (b) (4) are not considered relevant for the *in-vivo* performance. This claim indicates to an implied biowaiver request. Biopharm group in ONDQA will make a decision on approval of this biowaiver.

Chiral conversion in vivo

Linagliptin has one chiral center (see the chemical structure in **Figure 1** below). The R-enantiomer is used as active ingredient. In human plasma, following single oral administration of 600 mg linagliptin, only the parent compound with R-configuration was identified using enantioselective HPLC-MS/MS method. The enantiomeric excess of the R-enantiomer accounted for (b) (4) in humans.

On the contrary, for the main metabolite of linagliptin (i.e., CD1790), only the S-configuration was identified.

These results suggest that there was negligible chiral inversion of linagliptin *in vivo* in humans, if at all present, and that the formation of the corresponding S-configured alcohol CD 1790 was highly stereo selective.

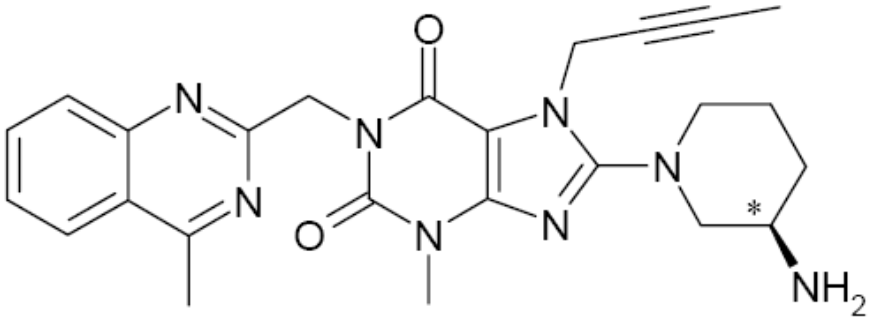


Figure 1: Chemical structure of linagliptin

Effect on QT interval
In a thorough QT study at single therapeutic (i.e., 5 mg) and single supra-therapeutic (i.e., 100 mg) dose no clinically relevant QT prolongation was observed. Also no clinically relevant changes in the heart rate, the uncorrected QT interval or other heart rate corrected QT intervals were observed compared to placebo.

Pediatrics development plan
A waiver has been request for evaluation of safety and effectiveness of linagliptin in age group ≤9 years. For age group 10-(b) (4) years, sponsor has requested deferral to ensure that sufficient safety and efficacy data were first collected in adult patients. No pediatric development plan has been submitted with this application.

Summary:
Summary of linagliptin PK
The PK characteristics of linagliptin are summarized in **Figure 2**. Sponsor states that linagliptin has high aqueous solubility and moderate permeability, suggesting that linagliptin would be classified as BCS Class 3 compound. After oral administration maximum concentrations (i.e., C_{max}) of linagliptin are reached in 1.5-2 hours. The absolute bioavailability of linagliptin after oral administration of 10 mg is approximately 30%. Data from preclinical studies and drug-drug interaction studies with ritonavir and rifampicin suggest that P-gp transporters limit the absorption of linagliptin from intestine. Following co-administration with food rate of absorption was reduced (median t_{max} increased from 1.02 to 2.99 hours and C_{max} was reduced by about 15% [CI: 75.9 to 94.6%]) but there was no effect on the extent of absorption.

Based on mass balance study, following oral administration, majority of drug was in form of parent compound in plasma (i.e., ~74%) and the proportion of main metabolite CD1790 was ~16.9%. In plasma linagliptin binds to DPP-4 in a concentration dependent manner, decreasing from 98.8% at 2 nM to 83% at 20 nM, reflecting saturation of binding to DPP-4 with increasing concentrations of linagliptin. Consequently the protein unbound fraction of linagliptin in plasma increases with increasing total plasma concentrations. ***As a result, linagliptin shows non-linear (less then dose proportional) PK both after oral and IV administration***, because the unbound fraction also remains accessible for metabolism and tissue distribution. In preclinical experiments linagliptin was tightly bound to peripheral tissues, which is assumed to be a result of binding to peripheral DPP-4. The volume of distribution at steady-state (V_{ss}) following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 liters. The formation of non-active plasma metabolite CD1790 (formed by CYP3A4) is dose dependent with decreasing relative exposure for lower linagliptin dose.

Because of its binding to DPP-4, terminal half-life of linagliptin is ~200 hours. However, this long half-life does not contribute to linagliptin's accumulation after multiple dosing. The accumulation half life of linagliptin is reported to be ~11.4 hours. After once-daily dosing, steady-state plasma concentrations of 5 mg linagliptin are reached by the third dose, with accumulation factors for C_{max} and AUC of about 1.3.

Metabolism is reported to be a minor pathway of elimination for linagliptin. Approximately 90% of administered dose gets excreted in feces as unchanged drug. The renal elimination is minor with <7% of administered dose eliminated by this route.

Linagliptin is a weak inhibitor of CYP3A4. Linagliptin was found to be a substrate for OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2, suggesting a possible OATP8-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and reabsorption of linagliptin *in vivo*. OATP2, OATP8 and OCTN1 activities were slightly inhibited by linagliptin at the highest concentration of 100 μM. Additionally, OCT1 and OATP2 activities were significantly inhibited with IC50% values of 45.2 μM and 69.7 μM, respectively. Given the micromolar concentrations of linagliptin that are needed for inhibition of the denoted SLC transporters it was assumed that a clinical drug-drug interaction is very unlikely.

The pharmacokinetics (PK) of linagliptin was reported to be consistent in healthy subjects and in patients with type 2 diabetes.

Summary of linagliptin population PK and PK-PD analysis

Sponsor conducted population PK analysis to assess the impact of covariates on linagliptin PK. Dense data after single-dose and steady-state from two Phase 1 studies (1218.2 and 1218.3) and sparse data from two Phase 2 studies (1218.5 and 1218.6) were used for this analysis. These studies evaluated the doses ranging from 0.5 mg to 10 mg in patients with T2DM. A semi-mechanistic model accounting for concentration dependent binding of linagliptin to DPP-4 was used to describe the PK. Log-transformation-both-side (LTBS) approach was used. Covariate effect was evaluated using GAM (generalized additive modeling) based on forward addition ($p \leq 0.01$) and backward elimination ($p \leq 0.001$) criteria. Model validation was performed using visual predictive checks (VPC) and posterior predictive checks (PPC). In this analysis body weight and add-on to metformin were found to be significant for bioavailability (F), dose and study/formulation for rate of absorption, and liver enzyme gamma-glutamyl-transpeptidase (GGT) for unbound clearance. In addition, estimated concentrations of central binding sites, likely reflecting DPP-4 concentrations, correlated with pre-dose DPP-4 activity, dose, age and gender. Overall impact of these covariates on linagliptin exposure was considered clinically irrelevant and no dose adjustments were recommended based on this analysis.

Sponsor also developed a population PK-PD model characterizing the relationship between linagliptin plasma concentrations and plasma DPP-4 activity. This analysis also evaluated the impact of intrinsic and extrinsic factors on this relationship. A sigmoid E_{max} model with hill coefficient was used. Parameters $IC_{50\%}$, $IC_{80\%}$, and baseline DPP-4 activity were calculated. Effect of covariates body weight, age, BMI, gender, GGT, ALT, FPG, cholesterol, and triglycerides on these parameters was assessed. It was found that females had slightly higher DPP-4 activity than males; and GGT, ALT, FPG, triglycerides and cholesterol were correlated with baseline DPP-4 activity. Combined effect of these covariates was reported to be minimal. The worst case scenario only changed the $IC_{50\%}$ from a minimum of 2.49 nM to a maximum of 4.13 nM and the $IC_{80\%}$ from a minimum of 4.44 nM to a maximum of 7.38 nM, respectively. As expected, DPP-4 inhibition was correlated with HbA1c and FPG. Also patients with higher baseline levels of FPG and HbA1c had higher reduction in these markers after treatment.

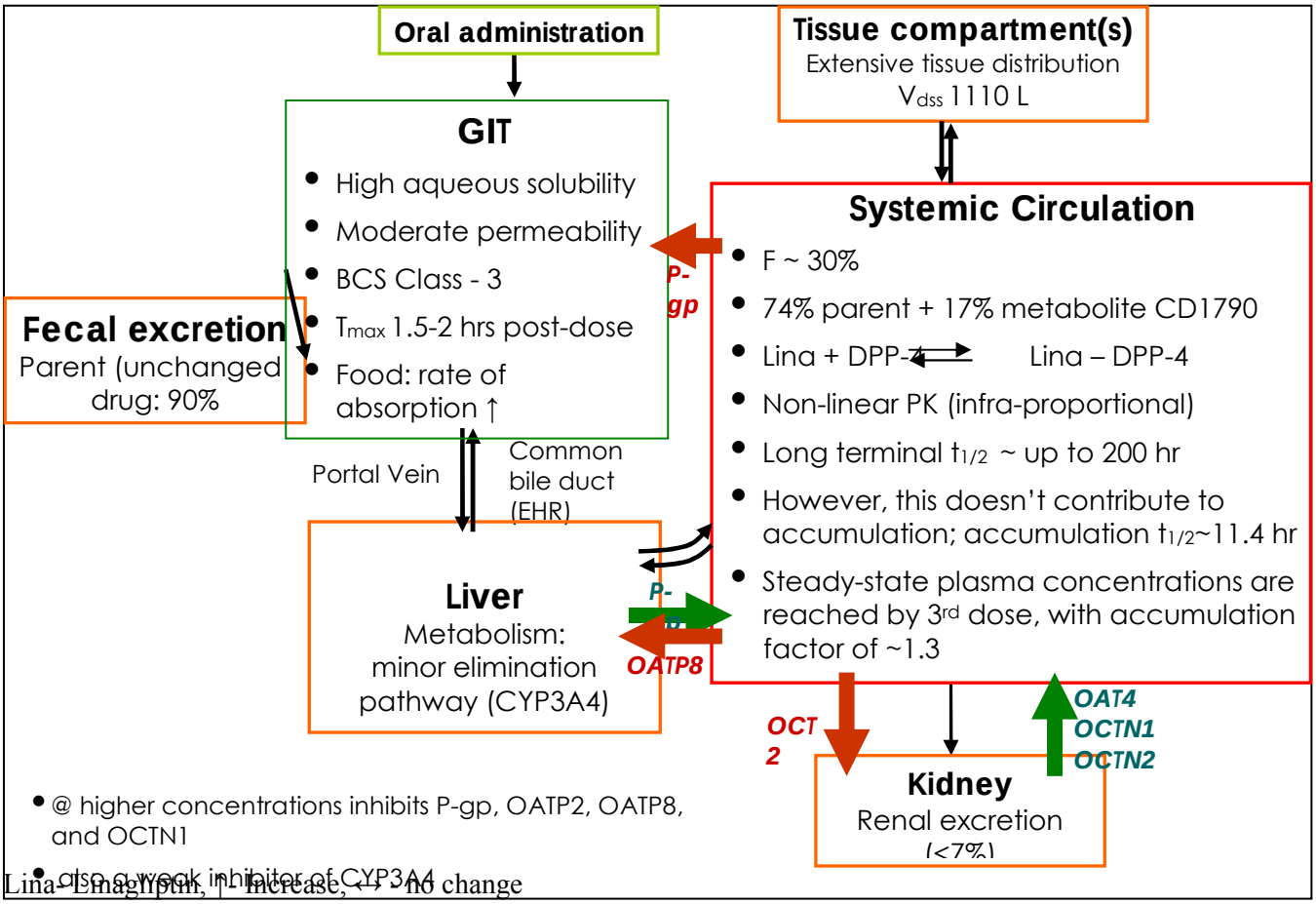


Figure 2: Schematic presentation of linagliptin PK properties

List of clinical pharmacology studies

Phase 1 studies in healthy subjects - - Single and multiple rising doses / Bioequivalence of different formulations

1218.1	Single rising dose (SRD)
1218.8	Food effect
1218.10	SRD - IV
1218.11	SRD & 2 week Multiple Rising Dose (MRD) - Japanese
1218.25	Bioavailability (comparison among TFII, TFIIb, iFF formulations)
1218.33	Dose proportionality
1218.34	Food effect
1218.45	Compare different dosing regimen 2.5 bid vs. 5 qd
1218.58	PK in Chinese

Phase 1 studies in healthy subjects -- Drug-drug interaction studies

1218.31	ritonavir
1218.67	rifampicin
1218.4	metformin
1218.13	pioglitazone

1218.30	glyburide
1218.9	simvastatin
1218.28	warfarin
1218.29	digoxin
1218.44	oral contraceptive

Phase 1 studies in healthy subjects -- ADME study

1218.7	^{14}C-human ADME- IV and oral

Phase 1 studies in healthy subjects -- Thorough QT study

1218.32	QT study at 5 mg and 100 mg dose

Phase 1 studies in patients with type 2 diabetes mellitus (T2DM)

1218.2	2 week MRD
1218.3	4 week MRD

Phase 1 study in subjects with renal impairment

1218.26	Study in patients with renal impairment

Phase 1 study in subjects with hepatic impairment

1218.27	Study in patients with hepatic impairment

Summary of drug-interaction studies

Effect of other drugs on linagliptin

Effect of co-administration of ritonavir, rifampicin, glyburide, metformin, and pioglitazone on linagliptin exposure (AUC) and C_{max} was evaluated. When given with ritonavir (a potent CYP3A4 and P-gp inhibitor) linagliptin AUC and C_{max} increased by 2- and 3-folds, respectively. With rifampicin (a potent CYP3A4 and P-gp inducer) both AUC and C_{max} decreased by ~40%. However, sponsor recommended no dose adjustments for these drugs citing large safety window for linagliptin. With glyburide, metformin, and pioglitazone change in AUC and C_{max} was less than 20%.

Effect of linagliptin on other drugs

Effect of linagliptin co-administration on simvastatin, digoxin, metformin, pioglitazone, warfarin, glyburide, and ethinylestradiol AUC and C_{max} was evaluated. No significant change in AUC and C_{max} was observed for any of the studied drug. It was concluded that at clinical concentrations, linagliptin is not an inhibitor of P-gp, OCT, CYP2C8, and CYP2C9. Inhibition of CYP3A4 by linagliptin is also negligible and no clinically meaningful drug interaction is expected with sulfonylureas.

Focus of clinical pharmacology review:

Clinical pharmacology review will focus on following key questions, in addition to other questions that may come up during the course of review.

- What are the PK characteristics of linagliptin after single dose and multiple doses (i.e., bioavailability, accumulation ratios, non-linearity, food effect, identification of metabolites and other ADME properties)?
- What is the impact of linagliptin on PD (i.e., DPP-4, FPG, HbA1c)
- Are linagliptin PK properties different between healthy volunteers and T2DM patients?

- Is the rational for selection of 5 mg dose appropriate?
- What is the exposure-response relationship for linagliptin for both efficacy and safety?
- Are the recommended dose adjustments for intrinsic and extrinsic factors appropriate?
- Are the bioanalytical methods for PK and PD markers appropriately validated?
- Is the conducted population PK analysis appropriate and are the dosing recommendations based on it justified?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201280	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	Linagliptin (BI 1356) Tablets.

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

/s/

LOKESH JAIN
08/27/2010

SALLY Y CHOE
08/27/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-280 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DMEP		
Sponsor:	Boehringer Ingelheim	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Linagliptin Film-coated IR Tablets	**Date Assigned:**	Jul 8, 2010
Indication:	Type 2 diabetes mellitus	**Date of Review:**	Aug 6, 2010
Formulation/strengths	IR Tablets, 5 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
July 2, 2010	July 7, 2010	Jul 8, 2010	May 2011
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications---**FILING REVIEW**		

REVIEW SUMMARY:

The sponsor has developed a formulation for linagliptin (an inhibitor of plasma dipeptidyl peptidase 4 activity) consisting of an immediate release (IR) film-coated tablet for the once daily treatment of type 2 diabetes mellitus. Linagliptin IR tablets will be marketed in the United States as 5mg IR Tablets. Linagliptin IR Tablet formulation used in the pivotal phase III clinical efficacy trial and safety trials is similar to the to-be-marketed formulation.

The dissolution method and specifications being proposed by the sponsor for linagliptin IR tablets based on the in vitro performance of BA/BE batches, clinical batches, and stability batches:

Drug Name	**Dosage Form**	**USP Apparatus**	**Speed (rpm)**	**Medium**	**Volume (mL)**	**Acceptance criteria**
Linagliptin	IR Tablet	I (Basket)	50	01N HCl	900, 37 °C ± 0.5 °C	Q=(b) (4) at 30 min

There are two differences in the chemical composition of the final to-be-marketed formulation (FF) and the formulation used in the clinical trials (iFF): (b) (4) according to FDA Guidance for Industry: Scale-up and post-approval changes (SUPAC-IR) and does not require a dissolution profile comparison or BE testing.

The sponsor provided complete information in support of the approval of the proposed dissolution method and specification consisting on dissolution method development information (effect of physicochemical properties, apparatus, agitation, dissolution media) and information on the discriminating power of the method. The acceptability of the dissolution method and specification and the role of dissolution in support of the manufacturing design space will be a review issue.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 201-280 (000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. There are no comments to the sponsor at this time.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

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

cc: ADorantes, RChiang, STran, ShMarkofsky, LJain;RChiang, Khushboo, OStephens

INTRODUCTION

The sponsor has developed a formulation for linagliptin (an inhibitor of plasma dipeptidyl peptidase 4 activity) consisting of an immediate release (IR) film-coated tablet for the once daily treatment of type 2 diabetes mellitus. Linagliptin IR tablets will be marketed in the United States as 5mg IR Tablets. Linagliptin IR Tablet formulation used in the pivotal phase III clinical efficacy trial and safety trials is similar to the to-be-marketed formulation.

(b) (4)

4 Pages have been Withheld as B4 (CCI/TS)
Immediately Following this Page

Reviewer's Comments

The acceptability of the proposed dissolution method and specifications will be a review issue.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201280	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	Linagliptin (BI 1356) Tablets.

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

/s/

SANDRA SUAREZ
08/09/2010

PATRICK J MARROUM
08/12/2010