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APPLICATION NUMBER:

201281Orig1s000

MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	10/15/2011
From	Ilan Irony, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/ Supplement#	201281/ Original submission
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	January 19, 2011
PDUFA Goal Date	November 19, 2011
Proprietary Name / Established (USAN) names	Proprietary name pending review / linagliptin / metformin fixed dose combination
Dosage forms / Strength	Oral Tablets in the following dose strengths: Linagliptin 2.5 mg / metformin 500 mg, Linagliptin 2.5 mg / metformin 850 mg and Linagliptin 2.5 mg / metformin 1000 mg
Proposed Indication(s)	Improve glycemic control in adults patients with T2DM
Recommended:	Complete Response

1. Introduction

This is an original New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The reference listed drug is the US approved labeling for Glucophage (metformin). The NDA is for a fixed dose combination tablet (FDC) of linagliptin, a dipeptidyl peptidase 4 inhibitor (DPP4-i) and metformin, the only member of the biguanide class. Both components are approved in the US. When this NDA was submitted to FDA for review (January 2011), the original linagliptin NDA was still under review. This NDA was therefore considered as new molecular entity. Since linagliptin was approved in May 2011, the FDC NDA is no longer a new molecular entity. As a FDC between two approved products, approval is dependent on demonstration of bioequivalence (BE) between the two components (linagliptin and metformin) and the FDC, regarding specified pharmacokinetic and pharmacodynamic characteristics.

2. Background

Linagliptin is the third DPP4-i approved in the US. It improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by inhibiting the inactivation of GLP-1 and GIP (incretin hormones) and prolonging the incretin effect on beta cells (serum glucose-dependent insulin stimulation) and alpha cells (glucagon suppression). GLP-1 in particular has other effects that contribute to improved glucose control in diabetics, such as appetite suppression and slowing of the rate of gastric emptying. Metformin is effective in decreasing hepatic glucose output and decreasing peripheral glucose utilization. Metformin gained a first line treatment recommendation by the American Diabetes Association and other diabetes professional organizations, and is widely used in the treatment of T2DM.

To support the approval of linagliptin under NDA 201280, the applicant has conducted Phase 2 and Phase 3 trials where the effect of linagliptin was assessed in subjects not adequately controlled with metformin alone. In addition, the applicant has demonstrated no drug-drug interaction between linagliptin and metformin. As a result of these aforementioned studies and their results, approval of a FDC for treatment of T2DM is dependent on demonstration of BE (geometric means ratio of C_{max} and AUC of linagliptin and metformin in the FDC to the same parameters measured when linagliptin and metformin are administered separately fall within an interval (e.g., 80 - 125%] that is unlikely to incur clinically significant variations). The FDC then is approved for either patients already taking both linagliptin and metformin separately, or for patients whose glycemic control remains inadequate despite treatment with either linagliptin or metformin. To allow treatment with the FDC in patients (b) (4) the applicant must show that the coadministration (or alternatively, the FDC) is more effective than each component alone, (b) (4) Such factorial study was conducted by BI and submitted under the current NDA for review.

3. CMC/Device

Refer to Dr. Markofsky's review for details of the CMC issues. CMC recommends a Complete Response, due to the Establishment Inspection recommendation. As of 11/7/11, the recommendation from the Office of Compliance/ Office of Manufacturing and Product Quality / Division of GMP Assessment was for Withhold for the (b) (4) manufacturing site, with an "Official Action Indicated" for that site.

The three dose strengths (linagliptin / metformin 2.5 mg / 500 mg, 2.5 mg / 850 mg and 2.5 mg / 1000 mg) are packaged in HDPE bottles in the following presentations: 14-count (for physician samples), 60-count (for one month supply), 180-count (for 3-month supply, and 2000-count (for mail-order pharmacies).

Besides linagliptin and metformin HCL, the drug product contains the following inactive ingredients: arginine, corn starch, copovidone, colloidal silicon dioxide, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc, yellow ferric oxide (2.5 mg/500 mg; 2.5 mg/850 mg tablets) and/or red ferric oxide (2.5 mg/850 mg; 2.5 mg/1000 mg tablets). All of the inactive ingredients are compendial.

Refer to linagliptin NDA 201280 for linagliptin drug substance information. Metformin hydrochloride (USP) is manufactured by (b) (4) BI referenced DMF (b) (4) for the CMC information related to the metformin HCl drug substance, and based on the Chemistry reviews of this DMF, this drug substance (metformin HCl) is adequate to support this NDA (201281). BI's specification and testing procedures also comply with the USP monograph for metformin HCl.

The stability studies support an expiration-dating period of 24 months for all strengths of the tablets when stored at room temperature [25°C (77°F)], with excursions permitted between 59 °F to 86°F (15°C to 30°C) packaged in all of the proposed commercial container closure systems. Consequently, a 24 month expiry is granted.

From a CMC standpoint, the initial recommendation for approval had been based on:

- Adequate information was provided in the NDA for the synthesis, purification and controls of the drug substances
- Adequate manufacturing information to support the proposed to-be-marketed drug product
- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability package to support the recommended expiry period of the drug product.

That initial recommendation was changed to a Complete Response as a result of the Office of Compliance recommendation for Withhold for one of the manufacturing sites.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology / toxicology team recommends approval of the NDA. Please refer to Dr. Carlson's review for details.

A single, 'proof of concept' study in diabetic mice showed a slight improvement in baseline fasting glucose and improved glucose excursion after oral glucose tolerance test (oGTT) with combined linagliptin and metformin treatment compared to either drug alone. The study was

limited to one week duration. Nevertheless, the diabetic mouse study supports the clinical finding of improved blood glucose control with coadministration of linagliptin plus metformin treatment over monotherapy treatments.

Nonclinical toxicology studies were conducted with coadministration of linagliptin and metformin, where linagliptin was given once daily. These studies did not identify any efficacy or safety endpoints that may be affected by a change from QD to BID dosing of linagliptin (same AUC_{0-24h} , with lower C_{max} compared to QD dosing).

Pivotal toxicity studies were conducted to bridge potential toxicity of the coadministration of linagliptin and metformin. No unexpected toxicity or significant supra-additive or synergistic interactions attributed to coadministration were identified that would alter previous pharmacology and toxicology conclusions about the safe use of linagliptin and metformin in the treatment of T2DM. Toxicity in nonclinical studies was driven by metformin, as expected based on dosing ratios and large safety margins with linagliptin. Major target organs of metformin were heart and liver, as evidenced by heart hypertrophy with immune cell infiltration/inflammation and liver hypertrophy with concomitant hepatic injury and elevated liver enzyme biomarkers, starting at approximately 10-times the expected clinical AUC exposures. Linagliptin coadministration did not have any apparent effect on heart, liver or other metformin-related toxicity on target organs including stomach and GI tract, salivary glands, lymphoreticular tissues, or reproductive tissues.

No carcinogenicity studies were conducted with linagliptin and metformin coadministration. Neither linagliptin nor metformin are genotoxic and neither is considered to pose a significant carcinogenic risk at clinical exposures. Several linagliptin impurities, including potential or theoretical impurities and degradants, were identified and adequately qualified to show no significant toxicologic or carcinogenic risk. No further carcinogenicity testing with the combined drugs is necessary.

A notable new toxicity issue was identified in the nonclinical program suggesting potential metformin-induced teratogenicity. Metformin is not listed as teratogenic at approximate clinical exposures (estimated based on body surface area) in current labels. Studies conducted by BI clearly demonstrated that metformin at 10- to 20-times human exposure caused skeletal malformations in Wistar Han rats (a rat species often used in European toxicology studies). The studies confirmed that metformin is not teratogenic at approximate clinical exposures (clear NOAELs were established). Linagliptin combination treatment did not have any remarkable effect on the metformin-related malformations. The use of Wistar Han rats seems significant because most embryofetal development studies are conducted in Sprague Dawley (SD) rats. The reference Glucophage® label does not note the rat strain used but it seems clear from the original pharmacology/toxicology review(s) that SD rats were used. Wistar rats are reported to be more sensitive to heart malformations than SD rats and they seem to be more susceptible to the rib and scapula malformations seen with metformin treatment. More importantly, metformin was clearly toxic to pregnant rats at the teratogenic doses, causing reduced body weight gain, modestly reduced plasma glucose (albeit not to marked hypoglycemic levels), and signs of metabolic acidosis (e.g., urine pH and serum electrolyte changes). Body weight decrements typically cause developmental delays (e.g., delayed skeletal ossification), but even maternal body weight loss does not seem to cause fetal malformations in rats. On the other hand, both hypoglycemia and metabolic acidosis are known to cause fetal malformations. Importantly, data from other DPP4 inhibitor development programs coadministered with metformin do not confirm metformin-induced skeletal malformations.

Several important trends were apparent from those recent studies: all were conducted in SD rats; all confirmed the absence of metformin teratogenicity at clinical exposures; all confirmed the absence of a significant effect of DPP4 inhibitor plus metformin combination treatment on embryofetal development; and, some of the studies confirmed metformin was not teratogenic at exposures up to approximately 10X MRHD.

The mechanism of metformin-induced teratogenicity was not investigated in this NDA. At the time of this writing, FDA has requested from the applicant evidence supporting the explanation that the malformations were related to hypoglycemia in the pregnant rats. Clearly there are differences in the embryofetal study results for this NDA compared to those described on the existing metformin labels and in other DPP4 inhibitor nonclinical programs. It is likely the maternal toxicity at teratogenic doses contributed to fetal findings, since there were no fetal malformations in the absence of metformin-induced maternal toxicity. It is equally important to emphasize that both metformin alone and the combined linagliptin plus metformin treatment were not teratogenic at approximate clinical exposures (by AUC), consistent with the current metformin label. Nevertheless, the teratogenicity findings at maternally toxic metformin doses in Wistar Han rats should be noted in the label for the proposed linagliptin plus metformin FDC tablets. Based on this conclusion, the Pharmacology / Toxicology team recommends a change in Pregnancy Category from the proposed “B” to a “C” category, while basically maintaining the descriptive language on bone malformations proposed by the applicant. However, FDA notified the applicant that information from adequate and well controlled clinical studies in pregnant women demonstrating that metformin is not a risk to the fetus may, upon review, support a designation of Pregnancy Category B. The applicant, in response, provided recent references regarding clinical trials and metaanalyses of the use of metformin in diabetic women during pregnancy, gestational diabetics and first trimester exposure in women with polycystic ovaries treated with metformin. We acknowledge the references to these clinical trials and metaanalyses, and believe they support a designation of Pregnancy Category B. The final descriptive language to summarize the clinical experience in the label is still under discussion, at the time of this writing.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

The Clinical Pharmacology 2 review team (OCP/DCP-2) recommends NDA approval. For details, please refer to Dr. Khurana’s clinical pharmacology review.

The key studies to support this NDA were:

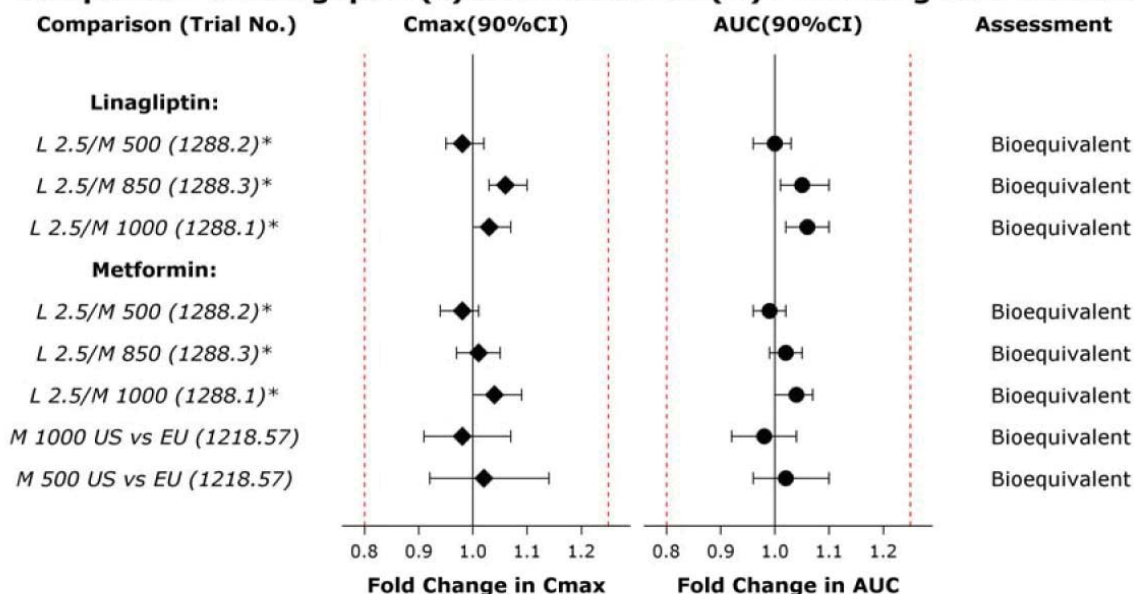
- Study 1288.1: BE between linagliptin 2.5 mg and metformin 1000 mg coadministration with linagliptin/metformin 2.5/1000 mg FDC
- Study 1288.2: BE between linagliptin 2.5 mg and metformin 500 mg coadministration with linagliptin/metformin 2.5/500 mg FDC
- Study 1288.3: BE between linagliptin 2.5 mg and metformin 850 mg coadministration with linagliptin/metformin 2.5/850 mg FDC
- Study 1218.57: BE between the EU sourced Glucophage® formulation (used in the pivotal Phase 3 trial and all BE studies) and the US approved Glucophage® formulation at 500 mg and 1000 mg dose strengths of metformin.

For the clinical pharmacology assessments, linagliptin and metformin were quantitated in plasma using validated HPLC-MS/MS assay methods. The assay methods were validated for analyzing these 2 analytes in plasma samples in terms of range, accuracy, precision and sensitivity.

BE was demonstrated between intended commercial FDC formulation and co-administration of individual tablet formulations for Linagliptin 2.5/Metformin 500 mg and Linagliptin 2.5/Metformin 1000 mg FDC. BE was also demonstrated between intended commercial FDC formulation and coadministration of individual tablet formulations for Linagliptin 2.5/Metformin 850 mg, and also between the EU sourced Glucophage® formulation and the US approved Glucophage® formulation (Figure 1).

Figure 1. Bioequivalence assessments between linagliptin/metformin FDC and individual components linagliptin and metformin, and between European sourced metformin and US-sourced metformin

Comparison of Linagliptin (L) and Metformin (M) PK Among Formulations



The horizontal axis show the fold change in Cmax and AUC relative to reference formulation

The red dashed reference lines on x-axis show the lower (0.8) and upper (1.25) BE limits

*Comparison of Fixed Dose Combination formulation versus individual components

Source: Dr. Khurana's Clinical Pharmacology review (Figure 2).

Labeling changes proposed by the clinical pharmacology review team to the FDC professional label language are consistent with the language used in the linagliptin and metformin approved package insert language.

Arindam Dasgupta, Ph.D., (Division of Bioequivalence and GLP Compliance [DBGC] / Office of Scientific Investigations [OSI] has conducted the following inspections related to studies 1288.1 and 1218.57:

Clinical site: Boehringer Ingelheim Pharma GmbH & Co. KG, in Germany;

Analytical sites:

(b) (4)

Following the above inspections, the Division of Bioequivalence and GLP Compliance recommends that the clinical (NAI) and analytical data (VAI) of studies 1288.1 and 1218.57 be accepted for Agency review.

Biopharmaceutics

Please refer to Dr. Mahayni's review for details. The focus of the Biopharmaceutics review is to evaluate the information/data supporting the proposed dissolution method, dissolution acceptance criteria, and manufacturing site change and provide a recommendation regarding their acceptability.

The dissolution method parameters and criteria for evaluation of linagliptin and metformin are acceptable. The dissolution data to support the change in manufacturing site is acceptable. The Biopharmaceutics reviewer recommends approval of the NDA.

6. Clinical Microbiology

There was no microbiology review. The product is not an antimicrobial and there are no issues regarding sterility.

7. Clinical/Statistical- Efficacy

Clinical Review

The clinical review team recommends approval of the NDA. For details, please refer to Dr. Kwon's clinical review of the NDA.

(b) (4) linagliptin/metformin FDC can be used in patients whenever treatment with both components is considered appropriate, (b) (4) (b) (4) the applicant conducted and submitted the results of a factorial design trial 1218.46 to demonstrate that initiating both components of the FDC in subjects who are treatment naïve provided superior glycemic control when compared to either linagliptin or metformin given as monotherapy.

This was a multinational, multicenter, Phase 3, randomized, double-blind, placebo-controlled parallel group trial to compare the efficacy and safety of twice daily coadministration of linagliptin 2.5 mg and metformin 500 mg or of linagliptin 2.5 mg and metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, BID) and linagliptin (5 mg, once daily [QD]) over 24 weeks in drug naïve or previously treated subjects (adequately washed out of the effect of their prior medications) with insufficient glycemic control. To be eligible, subjects in the treatment naïve category should have HbA1c in the range 7.5 to 11% and subjects previously treated with an oral antidiabetic drug should have an HbA1c in the range 7.5 to 10.5%. An uncontrolled, open-label arm evaluated the safety and efficacy of linagliptin and metformin (linagliptin 2.5 mg + metformin 1000 mg BID) for 24 weeks in subjects with poor glycemic control (HbA1c > 11%). The primary endpoint was the change in

HbA1c at week 24. Secondary endpoints frequently used in trials of T2DM were listed in the protocol.

Subjects who completed the randomized part of this trial without receiving rescue therapy were offered to participate in an extension trial (trial 1218.52).

A total of 791 subjects were randomized in 133 sites in Africa, Asia, Europe, North America, and South America in a 1:2:2:2:2 ratio to either placebo (72 subjects), linagliptin 5 mg (142 subjects), metformin 500 mg (144 subjects), metformin 1000 mg (147 subjects), linagliptin 2.5 mg and metformin 500 mg (143 subjects), or linagliptin 2.5 mg and metformin 1000 mg (143 subjects). Of the randomized subjects, 86.9 % completed the 24 weeks of trial duration. A total of 66 subjects entered the open-label arm of the trial and received linagliptin 2.5 mg and metformin 1000 mg.

The results in the full analysis set (FAS) demonstrated a statistically and clinically meaningful reduction with coadministration of linagliptin and metformin compared to the treatment with corresponding doses of monotherapy (Table 1). Table 1 also shows the glycemic-related secondary endpoints of proportion of subjects reaching HbA1c < 7% (a therapy goal recommended by the American Diabetes Association for adults with T2DM) and the proportion of subjects in each arm receiving glycemic rescue therapy (sulfonylurea, thiazolidinedione or insulin) based on protocol-defined criteria.

Table 1. Change in HbA1c (%) from baseline to week 24, responder analysis (proportion of subjects with HbA1c < 7%) and proportion receiving glycemic rescue in the FAS-LOCF population of Trial 1218.46

Study population	Placebo	Lina 5 mg Once Daily	Met 500 mg Twice Daily	Lina 2.5 mg + Met 500 mg Twice Daily	Met 1000 mg Twice Daily	Lina 2.5 mg + Met 1000 mg Twice Daily
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean, SE)	8.7 (0.1)	8.7 (0.1)	8.7 (0.1)	8.7 (0.1)	8.5 (0.1)	8.7 (0.1)
Change from baseline ¹ (SE)	0.1 (0.1)	-0.5 (0.1)	-0.6 (0.1)	-1.2 (0.1)	-1.0 (0.1)	-1.6 (0.1)
Diff from placebo ¹ (95% CI)	--	-0.6 (-0.8, -0.3)	-0.8 (-1.1, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Diff from Met alone ¹ (95% CI)				-0.6 (-0.8, -0.4)		-0.5 (-0.7, -0.3)
Diff from Lina alone ¹ (95% CI)				-0.8 (-1.0, -0.6)		-1.1 (-1.4, -0.9)
achieving A1C < 7% (n, %)*	7 (10.8)	14 (10.4)	27 (19.1)	44 (32.1)	43 (31.6)	76 (54.3)
Patients (% , n) receiving rescue medication	29.2 (19)	11.1 (15)	13.5 (19)	7.3 (10)	8.0 (11)	4.3 (6)

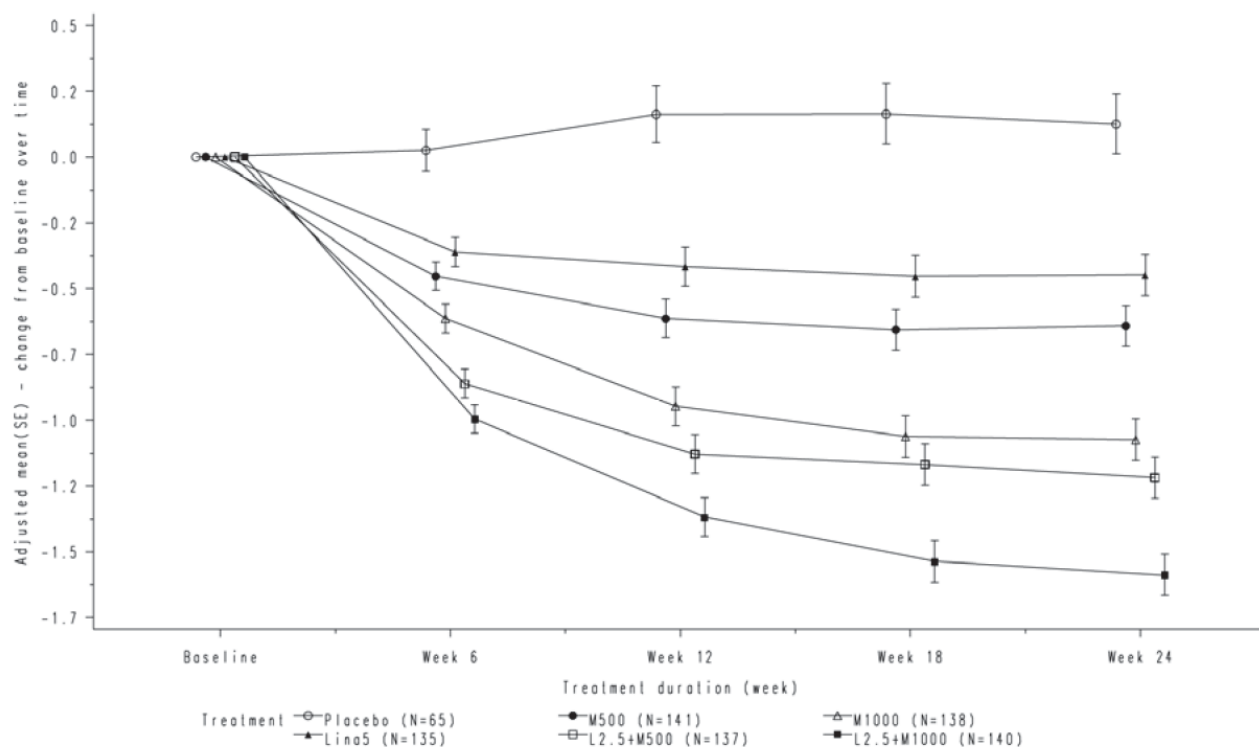
Source: Dr. Lui's statistical review.

Sensitivity analyses of the primary efficacy endpoint among completers (all subjects who completed 24 weeks of trial without glycemic rescue therapy) and among the per-protocol set (all randomized subjects without major protocol violations) yielded the same conclusions as the primary FAS/ITT analysis.

The treatment effect was consistent across different subgroups based on demographic and baseline disease characteristics.

In the open-label arm, the mean baseline HbA1c was 11.8 % at baseline and 7.9 % at the end of the trial, and the mean (SD) change from baseline to Week 24 was -3.7% (1.7). No formal hypothesis testing was done for this arm, as this was uncontrolled. (b) (4)

The graphical representation of changes in HbA1c over time for all controlled groups in the FAS dataset over the 24-week trial period is shown in Figure 2.

Figure 2. Change in adjusted mean HbA1c (%) from baseline over time - FAS (LOCF)

Source: Applicant's CTR 1218.46, Figure 15.2.1.2.2.1

Our statistical review team prefers that figures showing HbA1c changes over time in a trial be based on completer's data. Therefore we have requested that the applicant include in the label a figure based on completers, with regard to the results of the factorial trial 1218.46.

Change in fasting plasma glucose (FPG) from baseline to week 24, an important secondary endpoint to support the efficacy of coadministration of linagliptin and metformin, is shown in Table 2.

Table 2. Change in fasting plasma glucose (mg/dL) from baseline to week 24 in the FAS population in Study 1218.46

Treatment group	Number of patients, N (%) ²	FPG baseline, mean (SD)	Change in FPG from baseline		Difference to Lina/Met combination		
			Mean (SD)	Adjusted ¹ mean (SE)	Adjusted ¹ mean (SE)	95% CI	p-value
Placebo	61 (8.3)	203.3 (51.5)	6.0 (55.8)	10.2 (5.26)			
Lina 2.5 + Met 500 bid	135 (18.4)	198.6 (60.2)	-34.5 (49.5)	-33.2 (3.54)			
Met 500 bid	136 (18.5)	190.6 (46.6)	-13.4 (52.5)	-15.8 (3.52)	-17.4 (4.99)	(-27.2, -7.6)	0.0005
Lina 5 qd	134 (18.3)	195.3 (50.2)	-8.0 (46.8)	-8.6 (3.55)	-24.6 (5.01)	(-34.4, -14.8)	<0.0001
Lina 2.5 + Met 1000 bid	136 (18.5)	195.6 (50.4)	-49.5 (46.4)	-49.4 (3.52)			
Met 1000 bid	132 (18.0)	190.6 (52.2)	-30.2 (42.9)	-32.2 (3.58)	-17.2 (5.02)	(-27.1, -7.3)	0.0006
Lina 5 qd	134 (18.3)	195.3 (50.2)	-8.0 (46.8)	-8.6 (3.55)	-40.8 (5.00)	(-50.6, -31.0)	<0.0001

Lina = linagliptin; Met = metformin

¹ Model includes continuous baseline HbA_{1c}, continuous baseline FPG, prior use of anti-diabetic drugs, and treatment.² Patients in the FAS with a baseline FPG value and at least one on-treatment FPG value.

Source: Applicant's SCE, Table 3.2.1.2:1

Mean effects of the coadministration of linagliptin and metformin on the 2-hour glucose following a mixed meal tolerance test were small, but the trial was clearly underpowered to demonstrate an effect. Nonetheless, the individual components have been shown to have an effect on postprandial glucose, and there is no reason to suspect that the coadministration would not behave similarly.

Two clinical sites in India were inspected by the Division of Good Clinical Practice Compliance / OSI. The two sites contributed 54 subjects to trial 1218.46. While the final classification is pending, Dr. Leibenhaut's conclusion was that the clinical data in support of the NDA is considered reliable and should be accepted.

There were few data on the glycemic effect of linagliptin and metformin coadministration in the extension trial 1218.52, and the applicant has not proposed to include them in the current label, so I will not be discussing these data in the CDTL review memo.

Statistical Review

Please refer to Dr. Liu's review for details of the statistical review. The team recommends approval of the NDA. Study 1218.46 provided the only data included in the statistical review. In addition to the sensitivity analyses conducted by the applicant and reviewed by Dr. Kwon, Dr. Liu has conducted new analyses; among them the mixed-effects model repeated measures. The results from the sensitivity analyses (such as MMRM, completers, and per protocol) of the primary efficacy endpoint and the key secondary endpoint, FPG, support the superiority of the combination to placebo and to each corresponding component treatment on both HbA_{1c} and FPG reductions after 24 weeks treatment at a 0.05 level (two-sided).

In Dr. Liu's review, he noted that the efficacy of linagliptin 5 mg monotherapy compared to placebo in Trial 1218.46 through analyses other than FAS-LOCF was questionable, primarily due to a greater than average reduction in glycemic parameters in the placebo group (-0.3 to -0.4% mean change from baseline in the placebo group). This effect in Trial 1218.46 is inconsistent with the evidence supporting the efficacy of linagliptin 5 mg monotherapy as reviewed in the linagliptin NDA 201280: a 18-week trial and a 24-week trial have demonstrated placebo-adjusted changes in HbA1c (95% CI) of -0.6 % (-0.9, -0.3) and -0.7% (-0.9, -0.5), respectively, in a combined pool of 716 subjects, who were randomized 2:1 to linagliptin 5 mg versus placebo.

Subgroup analyses suggest that females derive greater benefit from the coadministration of linagliptin and metformin compared to males.

8. Safety

Of the clinical study reports submitted, only trials 1218.46 and 1218.52 were not previously reviewed under NDA 201280 for linagliptin.

A total of 3084 subjects with T2DM were exposed to the coadministration of linagliptin and metformin across Phase 2 and 3 trials of linagliptin, providing a total of 3006 patient-years of exposure.

There are no new safety issues related to the coadministration of linagliptin and metformin, based on Study 1218.46, the scant data from its extension study and the 4-month safety update. The only noteworthy exception is the metformin-related embryofetal malformations described in the reproductive toxicology studies using Wistar Han rats; refer to Dr. Carlson's pharmacology / toxicology review.

9. Advisory Committee Meeting

This linagliptin / metformin FDC NDA was not referred to an advisory committee because the drugs are not first in class and the safety profile is similar to that of other drugs approved for this indication. Evaluation of the safety data did not raise significant unexpected safety or efficacy issues. We concluded outside expertise was not necessary for this review.

10. Pediatrics

There is no need for new PREA-related PMRs for pediatric studies for this NDA. The approval letter will have a statement that refers to the existing linagliptin PREA PMRs (listed below): e.g., "We remind you of your requirements under PREA for....."), and that also indicates that these requirements apply to both forms of the drug.

PerRC, the Safety Requirement Team and Pediatric Maternal Health Staff concurred with this approach.

201280	Tradjenta (linagliptin)	A randomized, placebo-controlled, dose-finding study under PREA evaluating at least two doses of linagliptin as monotherapy in pediatric patients ages 10 to 16 years (inclusive).	Final Protocol: by 11/ 30/11 Trial Completion: by 2/28/14 Final Report Submission: by 8/31/14
201280	Tradjenta (linagliptin)	Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety, and pharmacokinetics of linagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive) as monotherapy and when added to metformin therapy.	Final Protocol: by 6/30/14 Trial Completion: by 3/31/17 Final Report Submission: by 9/30/17

11. Other Relevant Regulatory Issues

At the time of this writing, this application is being discussed by the 505(b)(2) clearance group in the Office of New Drugs. The main issue being discussed is that the reference listed drug in this NDA is Glucophage; however, we recommended the applicant incorporate the language describing metformin-related lactic acidosis and drug interactions to be based on the Glumetza label converted to conform to the Physician Labeling Rule and approved in April 2011.

12. Labeling

At the time of this CDTL memo, the proprietary name review by DMEPA is pending. The current trade name under consideration is Jentadueto; (b) (4) have been rejected by DMEPA.

Labeling is being discussed with the applicant, specifically for the summary description of metformin clinical trials used to support a Pregnancy Category “C” designation.

13. Recommendations/Risk Benefit Assessment

I recommend a Complete Response to the linagliptin / metformin FDC NDA. This fixed dose combination tablet is a convenience product, so that patients who need both linagliptin and metformin for glycemic control can take only one pill twice daily. But there are no additional risks for the FDC, compared to coadministration of these two drugs separately. Thus, this recommendation for action is based on the manufacturing inspection at one of the sites. The Office of Compliance had issued a “Withhold” recommendation for the (b) (4) site.

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/s/

ILAN IRONY

11/07/2011

This version was revised to reflect the OC/OMPQ recommendation.

MARY H PARKS

11/08/2011

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 201281
Priority or Standard	Standard
Submit Date(s)	January 19, 2011
Received Date(s)	January 19, 2011
PDUFA Goal Date	November 19, 2011
Division / Office	DMEP/ODE II
Reviewer Name(s)	Hyon J. Kwon, PharmD, MPH
Review Completion Date	October 14, 2011
Established Name	Linagliptin/Metformin
(Proposed) Trade Name	(b) (4)
Therapeutic Class	DPP4 inhibitor and biguanide
Applicant	Boehringer Ingelheim
Formulation(s)	Linagliptin (L)/Metformin (M) film-coated FDC tablets at dosages of 2.5 mg L/500 mg M, 2.5 mg L/850 mg M, and 2.5 mg L/1000 mg M
Dosing Regimen	Twice daily
Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM where treatment with linagliptin/metformin is appropriate
Intended Population(s)	Type 2 diabetes mellitus

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the linagliptin/metformin fixed dose combination (FDC) for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM).

1.2 Risk Benefit Assessment

Linagliptin (Tradjenta, NDA 201-280) has been approved for the treatment of T2DM in the US on May 2, 2011. Metformin (Glucophage, NDA 20-357) was approved for the treatment of T2DM on March 3, 1995. The applicant submitted a 505(b)(2) NDA for the following linagliptin/metformin FDC tablet strengths, with Glucophage as the reference listed drug (RLD):

- 2.5/500 mg to be given twice daily (BID)
- 2.5/850 mg to be given BID
- 2.5/1000 mg to be given BID

The applicant needed to demonstrate bioequivalence (BE) between linagliptin/metformin FDC and coadministration of linagliptin and metformin to bridge the existing safety and efficacy data from linagliptin and metformin NDA. Therefore, the pivotal studies were clinical pharmacology studies 1288.1, 1288.2, and 1288.3 that established BE by comparing the to-be-marketed linagliptin/metformin FDC product to the coadministration of linagliptin and metformin.

(b) (4) linagliptin/metformin FDC can be used in patients whenever treatment with both components is considered appropriate, (b) (4) (b) (4) the applicant conducted and submitted the results of a factorial design trial 1218.46 to demonstrate that initiating both components of the FDC in subjects who are treatment naive did not lead to unacceptable rates of adverse effects and provided superior glycemic control when compared to either linagliptin or metformin given as monotherapy. The primary endpoint was the change in HbA1c at week 24, and the results in the full analysis set (FAS) demonstrated a statistically and clinically meaningful reduction with coadministration of linagliptin and metformin compared to the treatment with corresponding doses of monotherapy:

- The coadministration of linagliptin 2.5 mg and metformin 1000 mg given twice daily (BID) resulted in a significant improvement in HbA1c (mean treatment difference, -0.5% [SE=0.11], $p<0.001$) when compared to metformin 1000 mg BID.
- The coadministration of linagliptin 2.5 mg and metformin 1000 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -1.1% [SE=0.11], $p<0.0001$) when compared to linagliptin 5 mg daily.

- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.6% [SE=0.11], $p<0.001$) when compared to metformin 500 mg BID.
- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.8% [SE=0.11], $p<0.0001$) when compared to linagliptin 5 mg daily.

The compiled safety data with coadministration of linagliptin and metformin did not indicate that coadministration pose an unacceptable rates of adverse effects when compared to the individual products. In clinical practice, T2DM are often treated by combining available therapies, and the availability of linagliptin/metformin FDC may allow some patients to reduce the number of pills needed to take to control their hyperglycemia. Thus the clinical benefit of having linagliptin/metformin FDC outweighs its risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I do not recommend any postmarket Risk Evaluation and Mitigation Strategies with linagliptin/metformin FDC.

1.4 Recommendations for Postmarket Requirements and Commitments

Several postmarketing studies are required under linagliptin (NDA 201-280), and I do not recommend any new postmarketing requirements or commitments for the linagliptin/metformin FDC. The required pediatric assessments under the Pediatric Research Equity Act (PREA) for linagliptin/metformin FDC can be met by fulfilling the required PREA studies under linagliptin NDA 201-280.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant submitted this 505(b)(2) NDA for linagliptin/metformin FDC as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. Glucophage is the reference listed drug (RLD) for metformin.

Linagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor, which prevents the degradation of incretin hormones such as glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). It was approved for the treatment of T2DM in the US on May 2, 2011 (NDA 201-280).

Metformin is an oral biguanide, which decreases production of hepatic glucose and improves insulin sensitivity. It was approved for the treatment of T2DM in US as Glucophage (NDA 20-357) on March 3, 1995.

The applicant proposes to develop the linagliptin/metformin FDC in the following strengths:

- 2.5/500 mg to be given BID
- 2.5/850 mg to be given BID
- 2.5/1000 mg to be given BID

Throughout the document, the following designations are used interchangeably:

- L or lina for linagliptin monotherapy; M or met for metformin monotherapy (e.g., linagliptin 5 mg daily is designated as L5, metformin 500 mg BID is designated as M500, metformin 1000 mg BID is designated as M1000)
- L+M, lina+met, and linagliptin+metformin for co-administration of linagliptin and metformin (e.g., linagliptin 2.5 mg + metformin 500 mg BID is designated as L2.5+M500, linagliptin 2.5 mg + metformin 1000 mg BID is designated as L2.5+M1000)
- L/M, lina/met, and linagliptin/metformin, for the FDC.

2.2 Tables of Currently Available Treatments for Proposed Indications

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and the following drug therapies, either alone or in combination:

- Biguanides: metformin (i.e., Glucophage)
- Sulfonylureas: glyburide (Micronase), glipizide (Glucotrol), glimepiride (Amaryl), chlorpropamide (Diabinese), tolazamide (Tolinase)
- Insulin
- GLP-1 agonist: exenatide (Byetta), liraglutide (Victoza)
- Thiazolidinediones (TZDs): rosiglitazone (Avandia), pioglitazone (Actos)
- Dipeptidyl peptidase 4 (DPP-4) inhibitor: sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta)
- Meglitinides: repaglinide (Prandin), nateglinide (Starlix)
- α -Glucosidase inhibitor: acarbose (Precose), miglitol (Glyset)
- Pramlintide (Symlin)
- Dopamine agonist: bromocriptine mesylate (Cycloset)
- Bile acid sequestrants: colestevlam (WelChol)
- Various fixed dose combinations of oral therapies (i.e., Janumet, ActoPlus Met, Kombiglyze XR)

2.3 Availability of Proposed Active Ingredient in the United States

Linagliptin (NDA 201-280) and metformin (Glucophage, NDA 20-357) have been approved for the treatment of T2DM in the US since May 2, 2011 and March 3, 1995 respectively.

2.4 Important Safety Issues With Consideration to Related Drugs

Labeled safety concerns with linagliptin include the following:

- Risk of hypoglycemia when used with an insulin secretagogue (e.g. sulfonylurea)
- Pancreatitis
- Nasopharyngitis

Labeled safety concerns with metformin include the following:

- Lactic acidosis; the risk increases with sepsis, dehydration, excessive alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure
- Contraindicated in patients with renal impairment (e.g., serum creatinine ≥ 1.5 mg/dL for males, ≥ 1.4 mg/dL for females, or abnormal creatinine clearance)
- When undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures requiring restricted intake of food and fluids.
- Vitamin B12 deficiency
- Hypersensitivity
- Hypoglycemia, in elderly and debilitated patients when caloric intake is deficient, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA meeting scheduled on March 16, 2010 was cancelled because our preliminary meeting comments and responses adequately addressed the applicant's questions. The applicant's questions and our responses were related to the format and content of their planned NDA submission. The applicant submitted this NDA in the agreed upon format and content from clinical perspective.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of submission was acceptable. The submission was organized and information was not difficult to find.

3.2 Compliance with Good Clinical Practices

The clinical trials not previously reviewed, 1218.46 and 1218.52, were conducted with Good Clinical Practice standards.

The Establishment Inspection Report (EIR) for the relevant manufacturing and testing facilities is still pending.

The DSI inspection of two requested clinical investigator sites in India for trial 1218.46 concluded that the data submitted by the applicant to support the requested indication should be considered reliable. However, the final classifications for both clinical sites are pending EIR.

3.3 Financial Disclosures

FDA Form 3454 was submitted by the applicant. Six studies (1218.17, 1218.18, 1218.20, 1218.46, 1218.52, and 1218.6) met the 21 CFR 54.2(e) definition of a “covered” clinical study for the purpose of financial disclosure.

There was one sub-investigator from trial 1218.52 who held financial interests requiring disclosure. This financial interest was listed as “national coordination fees for RELY trial paid to institution”. It is unlikely that this financial interest would alter the conclusion of this trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug product consists of linagliptin/metformin hydrochloride immediate-release (film coated) tablets, to be supplied in 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg strengths. These tablets are oval, debossed on one side with the company’s symbol and the other side with a symbol for strengths. The tablets are also distinguished by a characteristic color for each strength.

The applicant referenced their approved linagliptin tablets (NDA 201-280) for the CMC related to the linagliptin drug substance, which was found to be adequate to support this NDA by the Chemistry reviewer. For the CMC information related to the metformin hydrochloride drug substance, the applicant referenced DMF (b) (4) which was also found to be adequate to support this NDA by the Chemistry reviewer.

The applicant provided adequate drug product specifications, except for the dissolution specification in their initial submission. Biopharmaceutics determined that the dissolution data

did not support the applicant's proposed dissolution specification and sent comments to the applicant in the 74 day letter. The applicant responded to the 74 day letter with proposed specification of (b) (4) at 30 minutes for linagliptin and metformin, which was deemed acceptable by Dr. Houda Mahayani, Biopharmaceutics Reviewer.

The manufacturing process of linagliptin/metformin hydrochloride film-coated tablets was initially developed at Boehringer Ingelheim (BI)'s site in Biberach, Germany, and subsequently transferred to the intended commercial manufacturing site of BI in Ingelheim, Germany. The applicant provided comparative dissolution profiles of linagliptin/metformin hydrochloride film-coated tablets manufactured at the BI's Biberach site and at the BI's Ingelheim site, which showed that the dissolution profiles are not affected by the transfer of the manufacturing site.

Please see reviews written by Dr. Sheldon Markofsky and Dr. Houda Mahayani, Chemistry and Biopharmaceutics Reviewer respectively, for full details.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The toxicology data previously submitted to linagliptin and metformin (Tradjenta 201-280 and Glucophage 20-357 respectively) provide support for this linagliptin/metformin FDC NDA. To support the FDC, several new nonclinical studies were done with coadministration of linagliptin and metformin.

A single study in diabetic mice received treatment with coadministration of linagliptin and metformin and alone. A slight improvement in fasting glucose and improved glucose excursion was observed with combination therapy compared to monotherapy.

Pivotal toxicity studies to bridge the potential toxicity of combined linagliptin and metformin treatment demonstrated that there was no unexpected toxicity with the combined treatment. No carcinogenicity studies were conducted with coadministration of linagliptin and metformin since neither linagliptin nor metformin are genotoxic.

One notable new preclinical finding was a suggestion of potential metformin-induced teratogenicity. Metformin is not listed to be teratogenic in the current product labeling. The applicant's studies in Wistar Han rats showed that metformin caused skeletal malformations at 10 to 20 times the clinical exposure; no teratogenicity was observed at the clinical dose. The combined linagliptin and metformin therapy did not affect the metformin-related malformations. At the teratogenic doses of metformin, which was 10 times the expected clinical exposure, maternal toxicity was observed, which may have contributed to the fetal malformations.

Please refer to Dr. David Carlson's review for full details.

4.4 Clinical Pharmacology

The applicant aimed to establish the BE between the linagliptin/metformin FDC and the coadministration of linagliptin and metformin in order to bridge the existing safety and efficacy data from linagliptin (Tradjenta) and metformin (Glucophage). In order to achieve this, applicant conducted the following randomized, two-way crossover, fasted, single dose BE trials:

- Trial 1288.1, to evaluate the BE of the highest FDC dose strength (L2.5/M1000) to the respective single entity tablets.
- Trial 1288.2 to evaluate the BE of the lowest FDC dose strength (L2.5/M500) to the respective single entity tablets.
- Trial 1288.3 to evaluate the BE of the intermediate FDC dose strengths (L2.5/M850) to the respective single entity tablets.
- Trial 1218.57 to evaluate the BE between the European and the US metformin innovator products (Glucophage Merck and Glucophage BMS, respectively) at the dose strengths of 500 and 1000 mg, as European Glucophage was used in the factorial trial 1218.46.

The results of these pivotal pharmacology trials demonstrated that the linagliptin/metformin FDC was bioequivalent to the individual drugs combined.

Please refer to Dr. Manoj Khurana's clinical pharmacology review for complete details.

4.4.1 Mechanism of Action

Linagliptin/metformin contains two antihyperglycemic agents with each agent having a distinct mechanism of action that may lead to improved glucose homeostasis compared to monotherapy. Linagliptin inhibits the DPP-4 enzyme, therefore slowing the breakdown rate of GLP and GIP. GLP-1 lowers blood glucose by stimulating insulin secretion and decreasing hepatic glucose production. Metformin lowers blood glucose by decreasing hepatic glucose production and improving insulin sensitivity through peripheral glucose reuptake and utilization. Metformin does not directly affect insulin secretion or metabolism.

4.4.2 Pharmacodynamics

The currently approved dose for linagliptin is 5 mg daily, and the posology for linagliptin in the FDC is 2.5 mg given twice daily, to conform to the metformin posology. To support the linagliptin regimen in the FDC, the applicant evaluated the steady-state PK and PD of 16 subjects to compare linagliptin 5 mg daily to 2.5 mg twice daily in trial 1218.45. The mean plasma DPP-4 inhibition was comparable for both regimens over the 24-hour period, with both regimens demonstrating a mean plasma DPP-4 inhibition of $\geq 80\%$ over the 24 hour period. The average DPP-4 inhibition over a 24-hour interval at steady-state was similar for both dosage regimens (85.3% for 5 mg daily, 85.8% for 2.5 mg twice daily).

4.4.3 Pharmacokinetics

In order to support linagliptin twice daily regimen, the BE of linagliptin 5 mg daily to linagliptin 2.5 mg twice daily was demonstrated for 24-hour steady-state AUC ($AUC_{0-24,ss}$) in trial 1218.45, as shown in Table 1.

Table 1: 1218.45 - Comparison and 90% confidence interval of $AUC_{0-24,ss}$ between linagliptin 5 mg QD and 2.5 mg BID (N=15)

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

Source: 1218.45 Clinical Trial Report (CTR), Table 11.5.2:4

The results of three pivotal trials establishing the BE of each FDC dose strengths to the respective single entity tablets are summarized in Table 2.

Table 2: 1288.1, 1288.2, 1288.3: Comparison and 90% confidence intervals of $AUC_{0-\infty}$ (metformin), AUC_{0-72} (linagliptin), and C_{max} (both analytes)

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

Linagliptin 2.5 mg						
AUC ₀₋₇₂	94	95	99.9	96.6	103.3	13.9
C _{max}	94	95	98.1	94.4	101.9	16.0
Metformin hydrochloride 500 mg						
AUC _{0-∞}	94	95	99.1	96.4	102.0	11.6
C _{max}	94	95	97.9	94.4	101.5	14.9
Linagliptin 2.5 mg						
AUC ₀₋₇₂	95	94	104.0	100.2	108.0	15.4
C _{max}	95	94	105.9	102.7	109.3	12.9
Metformin hydrochloride 850 mg						
AUC _{0-∞}	95	93	101.2	98.3	104.1	11.8
C _{max}	95	93	99.8	96.2	103.6	15.4

Source: Module 2.7.1, Table 2.1:1, 2.2:1, 2.3:1

The BE of two strengths (500 and 1000 mg) of two different source metformin tablets (i.e., European [Merck] and US (BMS)) was established in trial 1218.57. The results for 1218.57 are summarized in Table 3.

Table 3: 1218.57 - Comparison and 90% confidence intervals of AUC_{0-∞} and C_{max}

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

Source: Module 2.7.1, Table 2.5:1

5 Sources of Clinical Data

The NDA 201281 was submitted in electronic Common Technical Document format, with the following link: <\\CDSESUB1\EVSPROD\NDA201281\201281.ENX>

The clinical development program for coadministration of linagliptin and metformin consists of 13 clinical studies, as listed in Table 4 in section 5.1: six Phase 1 trials, one Phase 2 trial, and six Phase 3 trials (2 of which are long-term extensions). Three trials (1218.20, 1218.40, and 1218.52) are still ongoing and the results of interim analyses are provided.

Of note, not included in the Table 4 below is trial 1218.57, which was conducted as part of the development of the FDC for linagliptin and metformin and showed bioequivalence between the European and US Glucophage reference products. The European Glucophage was used in trial 1218.46 and 1218.52. The results of 1218.57 are discussed in section 4.4 Clinical Pharmacology.

5.1 Tables of Studies/Clinical Trials

Table 4: Trials supporting the combination therapy with linagliptin and metformin

Study	Study design and duration	Treatments	N	Previously reviewed?
Phase 1				
1218.4	Randomized, open-label, multiple dose, crossover study	L 10 mg QD + M 850 mg TID	15	Yes; NDA 201280
1218.47	Randomized, open-label, single dose, crossover, relative bioavailability study	L2.5/M1000 vs L2.5+M1000	20	No
1288.1	Randomized, open-label, single dose, crossover, pivotal bioequivalence study	L2.5/M1000 vs L2.5+M1000	96	No
1288.2	Randomized, open-label, single dose, crossover, pivotal bioequivalence study	L2.5/M500 vs L2.5+M500	95	No
1288.3	Randomized, open-label, single dose, crossover, pivotal bioequivalence study	L2.5/M850 vs L2.5+M850	96	No
1288.4	Randomized, open-label, single dose, crossover, kinetic food interaction study	L2.5/M1000 with or without food	32	No
Phase 2				
1218.6	12-week, randomized, double-blind, placebo-controlled study with metformin as background	Placebo L5+M L10+M Glimepiride+M	71 66 66 65	Yes; NDA 201280
Phase 3				
1218.17	24-week, randomized, double-blind, placebo-controlled study with metformin as background	Placebo+M L5+M	177 523	Yes; NDA 201280
1218.18	24-week, randomized, double-blind, placebo-controlled study with metformin as background	Placebo+M+SU L5+M+SU	263 792	Yes; NDA 201280
1218.20	2-year, randomized, double-blind, active-controlled (glimepiride) study with metformin as background	Glimepiride+M L5+M	781 778	Yes; NDA 201280

1218.40	78-week, open-label extension of 1218.17 and 1218.18 with metformin as background	L5+M L5+M+SU	610 726	Yes; NDA 201280
1218.46	24-week, randomized, double-blind, placebo-controlled, factorial design, with treatment naive or washout	Placebo L5 M500 M1000 L2.5+M500 L2.5+M1000 L2.5+M1000 open-label	72 142 144 147 143 143 66	No
1218.52	54-week, randomized, double-blind, active-controlled extension study of 1218.46	M1000 L2.5+M500 L2.5+M1000	170 225 171	No

5.2 Review Strategy

The pharmacokinetics, safety, and efficacy profiles of linagliptin were reported and reviewed under NDA 201280 by the Medical Reviewer, Dr. Somya Dunn. I did not re-review the individual trials that were previously reviewed under linagliptin NDA 201280.

My efforts were concentrated in reviewing the new data or analysis from trials presented under the current NDA in support of FDC, mainly 1) the results of pivotal pharmacology trials showing bioequivalence between the FDC and coadministration of linagliptin and metformin, 2) the results of factorial trial for the combination therapy (1218.46) and its extension study (1218.52), and 3) analysis of pooled data for overall safety, with a focus on new data that were not previously reviewed under NDA 201280. The 4-month safety update, submitted by the applicant on May 18, 2011, was reviewed for the updated safety information.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Pivotal efficacy of the linagliptin + metformin combination (Trial 1218.46)

Trial 1218.46 was a pivotal, factorial Phase 3 trial to demonstrate the efficacy of the combination therapy. This was a multinational, multicenter, Phase 3, randomized, double-blind, placebo-controlled parallel group trial to compare the efficacy and safety of twice daily coadministration of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, BID) and linagliptin (5 mg, once daily [QD]) over 24 weeks in drug naive or previously treated type 2 diabetic patients with insufficient glycemic control. An open-label arm evaluated the safety and efficacy of linagliptin and metformin (linagliptin 2.5 mg + metformin 1000 mg BID) for 24 weeks in subjects with poor glycemic control. Subjects who completed the randomized part of this trial without receiving rescue therapy were offered to participate in an extension trial (trial 1218.52).

The primary objective of the randomized part of the trial was to investigate the efficacy and safety of linagliptin + metformin therapy compared to linagliptin or metformin alone given for 24 weeks to drug naive or previously treated T2DM subjects with insufficient glycemic control.

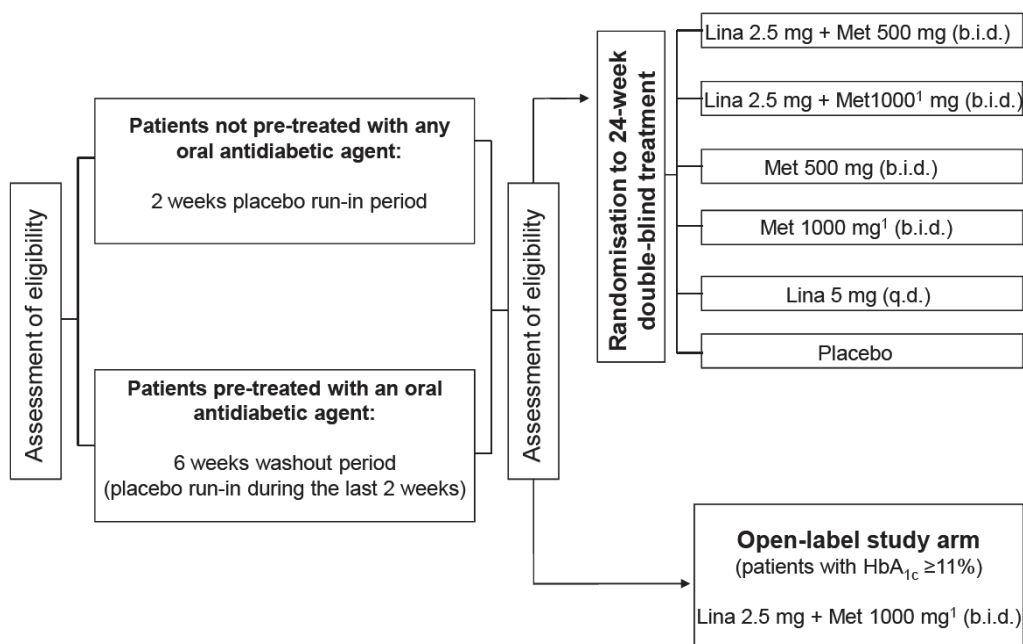
The primary objective of the open-label arm of the trial was to estimate the efficacy and safety of linagliptin and metformin in T2DM subjects with very poor glycemic control for 24 weeks.

Reviewer's comment: This factorial trial is important (b) (4)
Previous clinical trials where linagliptin 5 mg daily was added to metformin in T2DM subjects with insufficient glycemic control on metformin (trials 1218.17 and 1218.20) were important to support the linagliptin efficacy when added to the background metformin therapy.

Before randomization, subjects who were pre-treated with an oral antidiabetic drugs (metformin, sulfonylureas [SUs], DPP-4 inhibitors) stopped their oral antidiabetic drugs (OAD) and underwent a 4-week washout period and a 2-week placebo run-in period. If subjects were pre-treated with an excluded OAD (GLP-1 agonists or thiazolidinediones [TZDs]), subjects had an additional 6-week washout before the placebo run-in period. Subjects not pre-treated with an OAD (treatment-naïve) entered a 2-week placebo run-in period before randomization. All subjects who were to receive metformin 1000 mg underwent a 2-week forced titration phase for metformin.

Subjects who met the eligibility criteria after the run-in period were randomized to one of 6 treatment groups in a 1(placebo):2:2:2:2:2 ratio, and entered the 24-week treatment period, where they received either the co-administration of linagliptin plus metformin, the individual components of metformin, linagliptin 5 mg QD, or matching placebo (see Figure 1 below). The randomization was stratified by baseline HbA1c and number of prior OADs (none or monotherapy). Figure 1 shows an overview of the trial design.

Figure 1: Design overview of 1218.46



¹ Patients who received 1000 mg metformin had to undergo a 2-week forced titration

Source: 1218.46 CTR, Figure 9.2:1

Subjects were eligible for inclusion in the trial if they were 18 to 80 years of age, diagnosed with T2DM, had a body mass index (BMI) of $\leq 40 \text{ kg/m}^2$, and had insufficient glycemic control, which was defined as HbA1c 7.0 to 10.5% inclusive at Screening Visit for subjects pre-treated with one OAD, or HbA1c 7.5 to 11% inclusive for OAD-naïve subjects. Subjects who were previously treated were to not have received more than one other OAD, and the OAD had to be unchanged for 10 weeks before informed consent. All subjects were to have HbA1c from 7.5 to <11% at the start of run-in period. Patients with very poor glycemic control (HbA1c $\geq 11\%$) were enrolled into the open arm.

Subjects were not eligible to participate if they met any of the following key exclusion criteria:

- Myocardial infarction (MI), stroke, or transient ischemic attack (TIA) within 6 months prior to enrollment of the study; unstable or acute congestive heart failure
- Impaired hepatic function, defined as serum levels of alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), or alkaline phosphatase (ALP) above 3 x the upper limit of normal (ULN) at screening
- Treatment with TZDs, insulin, GLP-1 analogues, or anti-obesity drugs within 3 months prior to informed consent
- Treatment with systemic steroids at the time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent

- Renal failure or renal impairment at screening (estimated glomerular filtration rate [eGFR] <60 mL/min at screening)
- Drug- or alcohol-dependent or intolerant to any ingredient of the trial medications or the background medication
- Pre-menopausal women who are pregnant or nursing, or did not use adequate contraceptive methods

The use of rescue therapy with SUs, TZDs, or insulin was permitted during the treatment period if they met the rescue criteria, and subjects who received rescue therapy were followed in the trial.

The primary efficacy endpoint was the change from baseline in HbA1c after 24 weeks of treatment. For both the randomized groups and open-label arm, secondary endpoints included change from baseline in HbA1c and FPG by visit over time. For randomized groups only, secondary endpoints after 24 weeks of treatment included (1) occurrence of treat-to-target efficacy response (HbA1c on treatment <7% or <6.5%), (2) occurrence of relative efficacy response (HbA1c lowering by at least 0.5%), (3) change in FPG from baseline, (4) change in 2h-PPG from baseline (in the MTT subgroup), and (4) use of rescue therapy.

The safety endpoints included the incidence and intensity of adverse events (AEs), withdrawals due to AEs, clinically relevant changes in physical examination, vital signs, 12-lead electrocardiogram, and clinical laboratory assessments. In addition, all reported treatment-emergent fatal events and events suspected of stroke or cardiac ischemia, and cardiac death were reviewed regularly in a blinded fashion by an independent external committee (clinical event committee [CEC]), which consisted of cardiologists and neurologists. The frequency of subjects with the following CEC-confirmed events was also evaluated as safety endpoints: TIA, non-fatal stroke, non-fatal MI, other myocardial ischemia, and cardiovascular death (including fatal stroke).

The primary efficacy analysis was performed on the full analysis set (FAS), consisting of all treated subjects with valid measurements at baseline and at least one on-treatment measurement, with a last observation carried forward method (LOCF) for missing values for continuous variables (such as HbA1c, FPG, 2h-PPG). For binary variables (such as treat-to-target response of HbA1c<7%), missing values were considered as 'failures'. For sensitivity analysis, a subset of FAS, per-protocol set (PPS), consisting of subjects who did not have an important protocol violations that impacted efficacy, was analyzed. Another sensitivity analysis was done in the FAS-completers, which consisted of subjects in the FAS who completed and had an HbA1c measurement after 24 weeks of treatment without receiving rescue therapy. For safety evaluations, all subjects with at least one dose of study drug in the randomized period were included (the treated set). MTT was only performed in a subgroup of subjects (with voluntary site participation), and contains all subjects of the FAS with a valid MTT at baseline and at least one valid on-treatment MTT.

The superiority of linagliptin and metformin combined therapies compared to the respective monotherapies with regard to HbA1c change from baseline was tested using a sequential testing procedure at the level of $\alpha=0.05$ (2-sided). The sequential hierarchical procedure for testing null hypotheses was in the following order: (1) superiority of linagliptin 2.5 mg BID + metformin 1000 mg BID over metformin 1000 mg BID, (2) superiority of linagliptin 2.5 mg BID + metformin 1000 mg BID over linagliptin 5 mg QD, (3) superiority of linagliptin 2.5 mg BID + metformin 500 mg BID over metformin 500 mg BID, (4) superiority of linagliptin 2.5 mg BID + metformin 500 mg BID over linagliptin 5 mg QD. The analysis for the open-label arm was descriptive and there was no formal hypothesis being tested.

5.3.2 Long-term efficacy of linagliptin + metformin combination (Trial 1218.52, extension of 1218.46)

Trial 1218.52 was a Phase 3, multinational, multicenter, randomized, double-blind, parallel-group extension trial to evaluate the safety and efficacy of twice daily co-administration of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg compared to monotherapy with metformin 1000 mg BID over 54 weeks in subjects with T2DM who previously completed the week 24 of trial 1218.46 and were not on rescue therapy. This trial is still ongoing at the time of this NDA submission, and the applicant submitted data from interim analyses with the cut-off dates of June 8, 2010 in this NDA.

The objective of this trial was to investigate the safety and efficacy of linagliptin (2.5 mg plus metformin, either 500 mg or 1000 mg, BID) given for 54 weeks (2 week forced titration followed by 52 weeks of treatment). There was no primary hypothesis to be tested in this trial. Safety and tolerability were to be assessed in a descriptive analysis. The secondary endpoints were the same as trial 1218.46.

The original protocol only had two combination therapy group (lina 2.5 + met 500 or lina 2.5 + met 1000), and the protocol was amended (dated March 27, 2009) to include a third treatment group, met 1000¹. The assignment and re-randomization of subjects in the amended protocol is shown in Figure 2 below. Double-blind conditions were maintained during the transfer of subjects from trial 1218.46 to 1218.52.

¹ The applicant stated that this third treatment group, metformin 1000 mg, was added to fulfill new regulatory guidance (FDA Guidance for Industry on Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008) on long-term safety exposure in an appropriately controlled clinical trial design.

Figure 2: Randomization schedule in extension trial 1218.52

Randomised treatment in trial 1218.46 *†					
Linagliptin 2.5 mg plus metformin 500 mg b.i.d. (lina 2.5 + met 500)	Linagliptin 2.5 mg plus metformin 1000 mg b.i.d. (lina 2.5 + met 1000)	Metformin 1000 mg b.i.d. (met 1000)	Placebo*	Linagliptin 5 mg q.d.*	Metformin 500 mg b.i.d. (met 500)
↓	↓	↓	↓	↓	↓
Double-blind treatment in trial 1218.52					
Patients continue previous treatment			Patients randomised to 1 of 3 treatments as follows:		
lina 2.5 + met 500	lina 2.5 + met 1000	met 1000	lina 2.5 + met 500 or lina 2.5 + met 1000* or met 1000* (1:1:1 ratio)	lina 2.5 + met 500 or lina 2.5 + met 1000* (1:1 ratio)	lina 2.5 + met 500 or met 1000 (1:1 ratio)

* Patients not treated with metformin in trial 1218.46 who were randomised to treatment with metformin 1000 mg b.i.d. were to be treated with a lower dose of metformin (500 mg b.i.d.) for the first 2 weeks of this extension trial.

† Patients treated with open-label therapy in trial 1218.46 were not eligible to continue into this extension trial.

Source: CTR 1218.52, Figure 9.1:1

6 Review of Efficacy

Efficacy Summary

The applicant submitted linagliptin/metformin FDC for use as an adjunct to diet and exercise to improve glycemic control in T2DM patients. (b) (4)

The applicant plans to develop the following FDC strengths: linagliptin/metformin as 2.5/500 mg, 2.5/850 mg, and 2.5/1000 mg, to be given BID.

In order to bridge the existing safety and efficacy from linagliptin (Tradjenta) and metformin (Glucophage) to linagliptin/metformin FDC, the applicant needed to demonstrate BE between to-be-marketed linagliptin/metformin FDC and coadministration of linagliptin and metformin. This was achieved in three pivotal clinical pharmacology studies, 1288.1, 1288.2, and 1288.3. Also, since linagliptin is approved as 5 mg daily but in this FDC will be dosed 2.5 mg BID to follow metformin's posology, the applicant demonstrated BE of linagliptin 5 mg daily to 2.5 mg BID in 1218.45.

(b) (4)
they conducted a factorial design trial 1218.46 to demonstrate

that initiating both components of FDC in subjects who are treatment naive was superior when compared to the individual component of FDC. Trial 1218.46 was a multinational, multicenter, Phase 3, randomized, double-blind, placebo-controlled trial to compare the efficacy and safety of twice daily coadministration of L2.5+M500, L2.5+M1000, to the individual components of M500 BID, M1000 BID, and L5 QD. A total of 791 subjects were randomized 1:2 ratio of placebo to all the other active treatment arms.

The primary endpoint was the change in HbA1c at week 24, and the results in the FAS demonstrated a clinically meaningful reduction with combination therapies when compared to the treatment with corresponding doses of monotherapy:

- The coadministration of linagliptin 2.5 mg and metformin 1000 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.5% [SE=0.11], $p<0.001$) when compared to metformin 1000 mg BID
- The coadministration of linagliptin 2.5 mg and metformin 1000 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -1.1% [SE=0.11], $p<0.0001$) when compared to linagliptin 5 mg daily
- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.6% [SE=0.11], $p<0.001$) when compared to metformin 500 mg BID
- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.8% [SE=0.11], $p<0.0001$) when compared to linagliptin 5 mg daily

One of the secondary endpoints, FPG at week 24, also demonstrated that coadministration of linagliptin and metformin was superior to linagliptin or metformin alone.

6.1 Indication

The applicant proposed the following indication: “[TRADE] tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.”

Based on this NDA submission which contained the factorial trial, the applicant is proposing the (b) (4) indication for the FDC where linagliptin/metformin FDC can be used in patients whenever treatment with both components is considered appropriate, (b) (4)

6.1.1 Methods

In NDA 201280, the applicant provided the necessary data to support the efficacy and safety of linagliptin monotherapy, which included Phase 3 trials 1218.17, 1218.20, and 1218.40 (see Dr. Dunn’s review of NDA 201280 for complete details). The linagliptin NDA was approved on May 2, 2011.

All studies of linagliptin + metformin combination during Phase 3 clinical development were conducted with the coadministration of single components of linagliptin and metformin. The applicant provided results of important pharmacokinetic trials demonstrating bioequivalence between all three doses of to-be-marketed FDC and the coadministration of linagliptin 2.5 mg with metformin 500, 850, or 1000 mg, which are briefly summarized in section 4.4 Clinical Pharmacology.

In addition, (b) (4) (b) (4) the applicant conducted and submitted the results of a factorial trial 1218.46 to show that initiating both components of the FDC in patients who are treatment naive did not lead to unacceptable rates of adverse effects (e.g., hypoglycemia) and was a superior strategy compared to linagliptin or metformin given as monotherapy. See section 5.3.1 for description of design for trial 1218.46. In sections 6.1.2 through 6.1.7, the results of the pivotal factorial trial 1218.46 are presented.

The applicant also submitted an interim analysis for trial 1218.52, which is an extension trial of 1218.46, to demonstrate the long-term efficacy with the combined linagliptin and metformin therapy. The design of the trial 1218.52 is discussed in section 5.3.2, and the results are discussed in section 6.1.9.

The factorial trial 1218.46 did not test one of the proposed FDC dosage, linagliptin 2.5 mg/metformin 850 mg. The applicant propose to assume the efficacy for the linagliptin 2.5 mg + metformin 850 mg BID dose in the bracketing approach from trial 1218.46, and by providing the supportive data in the subset analysis of trial 1218.17. This subset analysis was reviewed in section 6.1.8.

6.1.2 Demographics

Randomized part:

Overall, the disease characteristics at baseline and demographic data were balanced among the treatment groups, as shown in Table 5. About half of subjects were males (53.9%), with the mean age of 55.3 years and the mean BMI of 29 kg/m². The mean age was 55.3 years, with the majority of subjects being <65 years of age (79%). Overall, 66.8% of subjects were White, 32.5% were Asian, and 0.6% were Black. The majority of subjects had a normal renal function or mild impairment (eGFR [calculated through the MDRD formula] 60 to <90 ml/min, 42.2%). Subjects between 65 and 74 years of age had a higher rate of mild renal impairment (68.5%) compared to subjects <65 years of age (35.4%).

Table 5: Baseline demographic data for 1218.46 - Treated set

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000	Total
Number of patients, N (%)	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
Gender, N (%)							
Male	36 (50.0)	80 (56.3)	82 (56.9)	78 (53.1)	73 (51.0)	77 (53.8)	426 (53.9)
Female	36 (50.0)	62 (43.7)	62 (43.1)	69 (46.9)	70 (49.0)	66 (46.2)	365 (46.1)
Race, N (%)							
Asian	26 (36.1)	45 (31.7)	51 (35.4)	50 (34.0)	37 (25.9)	48 (33.6)	257 (32.5)
Black	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.4)	1 (0.7)	5 (0.6)
Hawaiian/ Pacific Isle	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.1)
White	46 (63.9)	97 (68.3)	93 (64.6)	95 (64.6)	103 (72.0)	94 (65.7)	528 (66.8)
Ethnicity, N (%)							
Not Hisp/Lat	62 (86.1)	127 (89.4)	124 (86.1)	128 (87.1)	125 (87.4)	125 (87.4)	691 (87.4)
Hisp/Lat	10 (13.9)	14 (9.9)	20 (13.9)	18 (12.2)	18 (12.6)	18 (12.6)	98 (12.4)
Missing ¹	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.3)
Age [years]							
Mean (SD)	55.7 (11.0)	56.2 (10.8)	52.9 (10.4)	55.2 (10.6)	55.6 (11.2)	56.4 (10.7)	55.3 (10.8)
Age groups [years], N (%)							
<65	57 (79.2)	110 (77.5)	121 (84.0)	116 (78.9)	112 (78.3)	109 (76.2)	625 (79.0)
65 to 74	12 (16.7)	26 (18.3)	23 (16.0)	29 (19.7)	25 (17.5)	31 (21.7)	146 (18.5)
≥75	3 (4.2)	6 (4.2)	0 (0.0)	2 (1.4)	6 (4.2)	3 (2.1)	20 (2.5)
Baseline weight [kg]							
Mean (SD)	76.8 (17.5)	79.1 (17.3)	79.9 (18.4)	80.0 (18.5)	80.8 (19.0)	76.7 (16.0)	79.1 (17.8)
Baseline BMI [kg/m ²]							
Mean (SD)	28.62 (5.17)	28.95 (4.67)	28.92 (4.83)	29.52 (5.31)	29.66 (5.31)	28.55 (4.80)	29.08 (5.01)
Baseline eGFR (MDRD) ² [mL/min], N (%)							
≥90	36 (50.0)	67 (47.2)	81 (56.3)	79 (53.7)	70 (49.0)	76 (53.1)	409 (51.7)
60 to <90	27 (37.5)	70 (49.3)	52 (36.1)	60 (40.8)	62 (43.4)	63 (44.1)	334 (42.2)
30 to <60	2 (2.8)	2 (1.4)	4 (2.8)	1 (0.7)	2 (1.4)	1 (0.7)	12 (1.5)
Missing ³	7 (9.7)	3 (2.1)	7 (4.9)	7 (4.8)	9 (6.3)	3 (2.1)	36 (4.6)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

¹ Ethnicity data were not collected for patient 48171 (France) and patient 48731 (Netherlands).

² The degree of renal impairment was based on eGFR as calculated by the MDRD formula: none ≥90 mL/min, mild 60 to <90 mL/min, moderate 30 to <60 mL/min, and severe <30 mL/min.

³ For these patients, no valid baseline creatinine measurement was available; therefore the value was set to missing.

Source: CTR 1218.46, Table 11.2.1:1

Reviewer's comment: Similar to NDA 201280, the African American population was not well represented in this trial, as they comprised only 0.6% of total enrolled subjects, which is not reflective of general US type 2 diabetic patients. However, review of trials in linagliptin did not find any differences in efficacy and safety based on ethnicity (see Dr. Dunn's review of NDA 201280 for complete details).

The baseline efficacy variables and number of prior OADs are summarized in Table 6. The baseline HbA1c was comparable between all groups, with the overall HbA1c mean of 8.7%. The baseline FPG was slightly higher in the placebo group at 204 mg/dL, compared to the range of 191 to 199 mg/dL in the active treatment groups. About half of subjects were previously treated with one OAD (52.4%), and this was comparable across the groups. Metformin (38.5%) and SU (13.8%) were the most commonly used OADs prior to trial enrollment.

Table 6: Baseline efficacy variables and number of prior antidiabetic drugs - FAS

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000	Total
Baseline HbA _{1c} [%]							
Number of patients, N (%)	65 (100.0)	135 (100.0)	141 (100.0)	138 (100.0)	137 (100.0)	140 (100.0)	756 (100.0)
Mean (SD)	8.67 (0.95)	8.70 (0.97)	8.66 (0.90)	8.52 (0.87)	8.71 (0.95)	8.68 (1.03)	8.65 (0.94)
Baseline HbA _{1c} [%], categorical, N (%)							
Number of patients, N (%)	65 (100.0)	135 (100.0)	141 (100.0)	138 (100.0)	137 (100.0)	140 (100.0)	756 (100.0)
<7.0	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	1 (0.7)	2 (1.4)	5 (0.7)
7.0 to <8.0	18 (27.7)	36 (26.7)	32 (22.7)	45 (32.6)	36 (26.3)	34 (24.3)	201 (26.6)
8.0 to <9.0	21 (32.3)	55 (40.7)	57 (40.4)	47 (34.1)	49 (35.8)	55 (39.3)	284 (37.6)
≥9.0	26 (40.0)	44 (32.6)	51 (36.2)	45 (32.6)	51 (37.2)	49 (35.0)	266 (35.2)
Baseline FPG [mg/dL]							
Number of patients, N (%)	62 (100.0)	134 (100.0)	139 (100.0)	135 (100.0)	135 (100.0)	138 (100.0)	743 (100.0)
Mean (SD)	203.7 (51.2)	195.3 (50.2)	191.2 (46.9)	192.3 (52.8)	198.6 (60.2)	196.9 (51.2)	195.6 (52.3)
Number of prior OADs, N (%)							
Number of patients, N (%)	65 (100.0)	135 (100.0)	141 (100.0)	138 (100.0)	137 (100.0)	140 (100.0)	756 (100.0)
0	32 (49.2)	61 (45.2)	69 (48.9)	67 (48.6)	65 (47.7)	65 (46.4)	359 (47.5)
1	33 (50.8)	74 (54.8)	71 (50.4)	71 (51.4)	72 (52.6)	75 (53.6)	396 (52.4)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

Note that there was one patient (patient 47091) in the met 500 group who received 2 prior OADs (a combination therapy of metformin and SU), although only one prior OAD was permitted, this patient is counted separately; see also [Section 10.1](#) and [Table 15.1.4.2.1: 2](#).

Source: CTR 1218.46, Table 11.2.5:1

Table 7 below presents the length of time subjects were diagnosed with diabetes when they entered the trial (FAS). The majority of subjects had been diagnosed with T2DM for less than 5 years at baseline; overall, about 37% of subjects had diabetes for 1 year or less or >1 to <5 years. The placebo group appears to have been comprised of more subjects with longer history of diabetes in comparison to the active treatment groups, as the proportion of subjects with diagnosis of diabetes for more than 5 years was higher and subjects with diagnosis ≤ 5 years was lower in the placebo group compared to the active treatment groups. As expected, subjects 65 to 74 years of age tended to have diabetes for longer (50% for >5 years) compared to subjects <65 years of age (20% for >5 years).

Table 7: Time since diagnosis of diabetes at baseline - FAS

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000	Total
Number of patients, N(%)	65 (100.0)	135 (100.0)	141 (100.0)	138 (100.0)	137 (100.0)	140 (100.0)	756 (100.0)
Time since diagnosis of diabetes [years], N (%)							
up to 1	20 (30.8)	54 (40.0)	58 (41.1)	48 (34.8)	52 (38.0)	51 (36.4)	283 (37.4)
>1 to 5	23 (25.4)	47 (34.8)	50 (35.5)	63 (45.7)	46 (33.6)	50 (35.7)	279 (36.9)
>5	22 (33.8)	34 (25.2)	33 (23.4)	27 (19.6)	39 (28.5)	39 (27.9)	194 (25.7)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

Source: CTR 1218.46, Table 11.2.6:1

About 79% of subjects had one or more concomitant diagnosis at baseline, with a total of 13.1% having a cardiac disorder at baseline. The most frequently reported concomitant diagnosis were obesity (12.4%), hyperlipidemia (11.3%), and dyslipidemia (8.5%). Not unexpectedly, the rate of concomitant diagnoses increased with increasing age: 85.6% in 65 to 74 years age group versus 76.6% in <65 years age group.

Table 8 shows differences among the treatment groups with regard to concomitant diagnoses related to diabetes at baseline. The majority of subjects had a baseline diagnosis of metabolic syndrome according to the IDF definition (54.1%) and hypertension (53.5%). The proportion of subjects who had microvascular and macrovascular disease and metabolic syndrome was higher in the placebo group compared to the active treatment groups.

Table 8: Concomitant diagnoses related to diabetes at baseline - Treated set

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000	Total
Number of patients, N (%)	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
Patients with, N (%)							
Microvascular disease ¹	17 (23.6)	23 (16.2)	19 (13.2)	23 (15.6)	17 (11.9)	14 (9.8)	113 (14.3)
Macrovascular disease ²	48 (66.7)	85 (59.9)	72 (50.0)	79 (53.7)	81 (56.6)	71 (49.7)	436 (55.1)
Diabetic foot	0 (0.0)	1 (0.7)	4 (2.8)	0 (0.0)	0 (0.0)	1 (0.7)	6 (0.8)
Metabolic syndrome ³	45 (62.5)	69 (48.6)	76 (52.8)	81 (55.1)	83 (58.0)	74 (51.7)	428 (54.1)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

Note that a patient could have more than one concomitant diagnosis related to diabetes at baseline.

¹ including diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy

² including coronary artery disease, peripheral artery occlusive disease, cerebrovascular disease, and hypertension

³ The presence of metabolic syndrome at baseline was assessed by the investigators based on the IDF consensus worldwide definition [R06-0919]. According to this definition, a person has the metabolic syndrome if he or she has central obesity (waist circumference ≥ 94 cm for Euroid men and ≥ 80 cm for Euroid women, with specific values for other groups) plus any 2 of the following 4 factors: raised triglyceride level (≥ 150 mg/dL) or specific treatment for this lipid abnormality; reduced HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females) or specific treatment for this lipid abnormality; raised blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) or treatment of previously diagnosed hypertension; raised FPG ≥ 100 mg/dL or previously diagnosed T2DM.

Source: CTR 1218.46, Table 11.2.6:2

Open arm: In the open-label arm, there were more females (60.6%) than males (39.4%). Only White (63.6%) and Asian subjects (36.4%) participated in the open arm. Table 9 provides further details of all the demographic data in the open arm.

Table 9: Demographic data - Open Label Arm

	L2.5+M1000
<=70 kg	27 (40.9)
>70-80 kg	11 (16.7)
>80-90 kg	14 (21.2)
>90 kg	14 (21.2)
Baseline BMI [kg/m2],	
N	66
Mean	28.81
SD	4.93
Min	19.04
Median	29.36
Max	38.20
Baseline BMI (categorical) [N (%)]	
<25	18 (27.3)
25-<30	20 (30.3)
≥30	28 (42.4)
Baseline eGFR according to MDRD, [ml/min], [N (%)]	
≥90 (normal renal function)	41 (62.1)
60 to <90 (mild renal impairment)	20 (30.3)
30 to <60 (moderate renal impairment)	2 (3.0)
<30 (severe or endstage renal impairment)	0 (0.0)
Missing	3 (4.5)
Baseline eCCR (Cockroft-Gault), [ml/min], [N (%)]	
≥80 (normal renal function)	53 (80.3)
50 to <80 (mild renal impairment)	10 (15.2)
30 to <50 (moderate renal impairment)	0 (0.0)
<30 (severe or endstage renal impairment)	0 (0.0)
Missing	3 (4.5)

Source: CTR 1218.46, Table 15.1.4.1.2:1

6.1.3 Subject Disposition

A total of 1770 subjects were screened, and 913 subjects were not randomized. The most common reason for not being randomized was not meeting inclusion/exclusion criteria (42.8% of subjects screened out), mostly due to not meeting the HbA1c criteria at either screening visit or at the start of run-in period, followed by other reasons (4% of subjects screened out), and consent withdrawal (3.8% of subjects screened out).

A total of 791 subjects were randomized by 133 centers in Africa, Asia, Europe, North America, and South America in a 1:2:2:2:2 ratio to either placebo (72 subjects), linagliptin 5 mg (142 subjects), metformin 500 mg (144 subjects), metformin 1000 mg (147 subjects), linagliptin 2.5 mg + metformin 500 mg (143 subjects), or linagliptin 2.5 mg + metformin 1000 mg (143 subjects). All randomized subjects were treated. A total of 66 subjects entered the open-label

arm of the trial and received linagliptin 2.5 mg + metformin 1000 mg. Table 10 below shows the overall disposition of subjects in the trial.

Nearly half of the total subjects were randomized in Europe (47.4%), with the largest proportion of subjects originating from Russia (8.1%) and France (8.0%). About one third of the total subjects were randomized in India (31.5%).

Table 10: Overall disposition of subjects in 1218.46

	Placebo N (%)	M500 N (%)	M1000 N (%)	Lina5 N (%)	L2.5+M500 N (%)	L2.5+M1000 N (%)	Total N (%)
Enrolled							1770
Started wash-out							598
Started placebo run-in							957
Not randomised							913
Open label							66
Randomised	72	144	147	142	143	143	791
Not treated	0	0	0	0	0	0	0
Treated *	72 (100.0)	144 (100.0)	147 (100.0)	142 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
Not prematurely discontinued trial medication	54 (75.0)	127 (88.2)	126 (85.7)	121 (85.2)	127 (88.8)	132 (92.3)	687 (86.9)
Prematurely discontinued trial medication	18 (25.0)	17 (11.8)	21 (14.3)	21 (14.8)	16 (11.2)	11 (7.7)	104 (13.1)
Adverse events	3 (4.2)	4 (2.8)	6 (4.1)	6 (4.2)	5 (3.5)	2 (1.4)	26 (3.3)
AE study dis. worse	1 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
AE other dis. worse	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.3)
AE other	2 (2.8)	3 (2.1)	5 (3.4)	5 (3.5)	5 (3.5)	2 (1.4)	22 (2.8)
Lack of efficacy #	6 (8.3)	4 (2.8)	2 (1.4)	3 (2.1)	1 (0.7)	2 (1.4)	18 (2.3)
Non compl. protocol	2 (2.8)	1 (0.7)	3 (2.0)	3 (2.1)	3 (2.1)	2 (1.4)	14 (1.8)
Lost to follow-up	1 (1.4)	3 (2.1)	4 (2.7)	3 (2.1)	4 (2.8)	0 (0.0)	15 (1.9)
Refused cont. medic.	5 (6.9)	4 (2.8)	5 (3.4)	4 (2.8)	2 (1.4)	3 (2.1)	23 (2.9)
Other	1 (1.4)	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	2 (1.4)	8 (1.0)

* In all tables 'treated' refers to treatment with randomised study drug

Includes patients discontinued due to hyperglycemia

Source: CTR 1218.46, Table 15.1.1:1

Of 791 randomized subjects, 86.9% completed the 24-week duration of trial and 13.1% prematurely discontinued the trial. Overall, the most frequent reasons for discontinuation were adverse events (3.3%), refusal to continue trial drug (2.9%), and lack of efficacy (2.3%). The premature discontinuation rate was higher in the placebo group compared to the active treatment groups, and this difference appeared to be due to higher rate of discontinuations due to lack of efficacy (8.3%) and refusal to continue trial drug (6.9%) in the placebo group.

Reviewer's comment: There was a small discrepancy in the number of subjects who prematurely discontinued the trial due to adverse events (AEs) in Table 10 versus Table 29 in the placebo (3 versus 5), M500 (4 versus 3), and L2.5+M1000 arms (2 versus 3). It is possible that these subjects were misclassified into another reason for premature trial discontinuation, and this small discrepancy does not alter the overall safety of combined linagliptin and metformin therapy. In addition, the review of the AEs leading to discontinuation in these arms, as summarized in Table 29, did not reveal a significant finding that is of concern.

Table 11 displays the distribution of subjects for different analysis sets to be used for evaluating efficacy and safety. All efficacy endpoints were analyzed using the FAS, and sensitivity analyses were done in the PPS and the FAS-completers. These data sets were defined in section 5.3.1.

Table 11: Number of subjects by analysis set

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Randomised set	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
Treated set	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
FAS	65 (90.3)	135 (95.1)	141 (97.9)	138 (93.9)	137 (95.8)	140 (97.9)	756 (95.6)
FAS-completers	52 (80.0)	118 (87.4)	120 (85.1)	122 (88.4)	125 (91.2)	129 (92.1)	666 (88.1)
PPS	63 (96.9)	130 (96.3)	140 (99.3)	129 (93.5)	133 (97.1)	135 (96.4)	730 (96.6)
MTT set	9 (13.8)	16 (11.9)	17 (12.1)	15 (10.9)	12 (8.8)	15 (10.7)	84 (11.1)
OLS	--	--	--	--	--	--	66

FAS = full analysis set, MTT = meal tolerance test, OLS = open-label set, PPS = per-protocol set

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

Source: CTR 1218.46, Table 11.1:1

6.1.4 Analysis of Primary Endpoint - HbA1c

Randomized part:

The primary endpoint was the change in HbA1c from baseline after 24 weeks of treatment, which was analyzed using an analysis of covariance (ANCOVA) with treatment and the use of prior anti-diabetic drugs as fixed factors and baseline HbA1c as linear covariate. The baseline HbA1c was defined as the last available HbA1c before the start of randomized study drug, excluding values before the start of a potential washout period. HbA1c values were regarded as “on-treatment” if they were obtained after the first dose of study drug and up to 7 days after the last dose of study drug.

The results of the primary analysis in the FAS population are summarized in Table 12 below. The treatment difference in HbA1c from baseline to Week 24 with linagliptin monotherapy compared to placebo was -0.6% (95% CI -0.9, -0.3; p<0.0001).

Table 12: Differences between adjusted means for HbA_{1c} change from baseline at Week 24 - FAS (LOCF)

Treatment group	Number of patients, N (%)	HbA _{1c} baseline, mean (SD)	Change in HbA _{1c} from baseline		Difference to Lina/Met combination		
			Mean (SD)	Adjusted ¹ mean (SE)	Adjusted ¹ mean (SE)	95% CI	p-value
Placebo	65 (8.6)	8.67 (0.95)	0.13 (1.17)	0.13 (0.11)			
Lina 2.5 + Met 500 bid	137 (18.1)	8.71 (0.95)	-1.22 (0.98)	-1.22 (0.08)			
Met 500 bid	141 (18.7)	8.66 (0.90)	-0.63 (1.05)	-0.64 (0.08)	-0.58 (0.11)	(-0.79, -0.36)	<0.0001
Lina 5 qd	135 (17.9)	8.70 (0.97)	-0.43 (1.05)	-0.45 (0.08)	-0.77 (0.11)	(-0.99, -0.55)	<0.0001
Lina 2.5 + Met 1000 bid	140 (18.5)	8.68 (1.03)	-1.57 (0.98)	-1.59 (0.08)			
Met 1000 bid	138 (18.3)	8.52 (0.87)	-1.02 (1.01)	-1.07 (0.08)	-0.51 (0.11)	(-0.73, -0.30)	<0.0001
Lina 5 qd	135 (17.9)	8.70 (0.97)	-0.43 (1.05)	-0.45 (0.08)	-1.14 (0.11)	(-1.36, -0.92)	<0.0001

Lina = linagliptin; Met = metformin; SE = standard error (of the mean)

¹ Model includes continuous baseline HbA_{1c}, prior use of anti-diabetic drugs, and treatment.

Source: SCE, Table 3.2.1.1:1

The sensitivity analyses on the primary endpoint were conducted in the PPS and FAS-completers, and showed similar differences between the treatment groups in the adjusted mean HbA_{1c} changes from baseline to Week 24 with all p-values <0.0001, confirming the results of the primary analysis. The results of the secondary analysis in the FAS-completers are shown in Table 13.

Table 13: Adjusted means for HbA1c (%) change from baseline at Week 24 - FAS-completers (OC)

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	38	107	116
Baseline unadjusted mean (SD)	8.46 (0.94)	8.51 (0.86)	8.46 (0.86)
End of study adjusted mean (SE)	8.27 (0.13)	7.79 (0.08)	7.35 (0.08)
Change to end of study adjusted mean (SE)	-0.28 (0.13)	-0.76 (0.08)	-1.20 (0.08)
Lina 5 od/ Lina 2.5 bid*			
N	108	117	124
Baseline unadjusted mean (SD)	8.61 (0.94)	8.63 (0.87)	8.57 (0.98)
End of study adjusted mean (SE)	8.04 (0.08)	7.28 (0.08)	6.88 (0.07)
Change to end of study adjusted mean (SE)	-0.51 (0.08)	-1.27 (0.08)	-1.67 (0.07)
Difference to Met component		-0.51 (0.11)	-0.46 (0.11)
95% CI		(-0.73, -0.30)	(-0.67, -0.25)
p-value		<.0001	<.0001
Difference to Lina 5		-0.76 (0.11)	-1.15 (0.11)
95% CI		(-0.97, -0.54)	(-1.37, -0.94)
p-value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
Model includes treatment, continuous baseline HbA1c and prior OADs
Difference in the number of patients in the analysis set and analysed are due to intake of rescue medication

Source: 1218.46 CTR, Table 15.2.1.2.1:2

Open-label arm:

In the open-label arm, the mean baseline HbA1c was 11.84% at baseline and 7.90% at the end of study, and the mean change from baseline to Week 24 was -3.7% (SD 1.7). No formal hypothesis testing was done for this arm, as this was an open-label arm to estimate the efficacy of the combination therapy in T2DM subjects with very poor glycemic control.

Reviewer's comment: The subjects treated with open-label L2.5+M1000 had greater reductions in HbA1c compared to the double-blind L2.5+M1000 group, which is not surprising since the subjects in the open-label arm had a higher baseline HbA1c. Subjects with higher baseline HbA1c will respond, on average, with greater reduction in their HbA1c with effective treatment.

6.1.5 Analysis of Secondary Endpoints

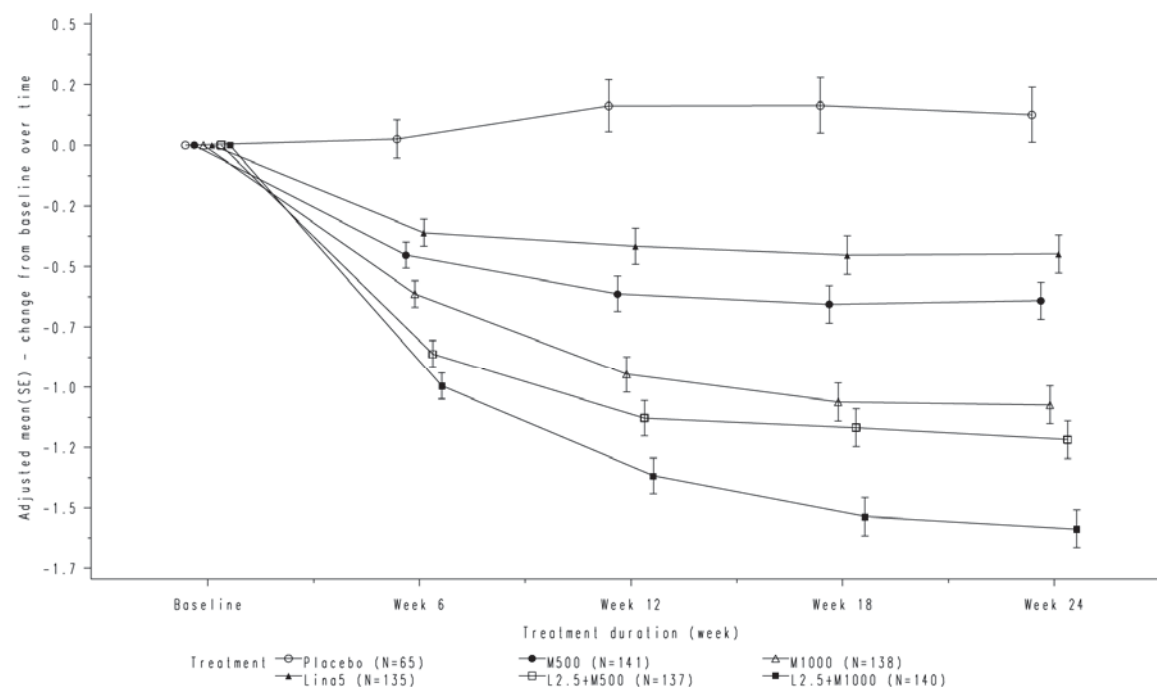
All the secondary endpoints discussed in this section are applicable for the randomized groups. The only secondary endpoints for the open-label arm are HbA1c change from baseline by visit over time and the change from baseline in FPG by visit over time.

6.1.5.1 Change in HbA1c from baseline by visit over time

Randomized arms: The mean change in HbA1c from baseline over time was analyzed using the same model as for the primary efficacy endpoint. From baseline to Week 24, at each visit, a greater reduction in the adjusted mean change in HbA1c were seen in the combination treatment arms compared to the individual metformin and linagliptin component arms, with all p-values

<0.0001 for each comparison. Figure 3 displays the change in adjusted mean HbA1c change from baseline over time, showing a continuous decrease from baseline to Week 24 in HbA1c in the active treatment groups.

Figure 3: Change in adjusted mean HbA1c (%) from baseline over time - FAS (LOCF)

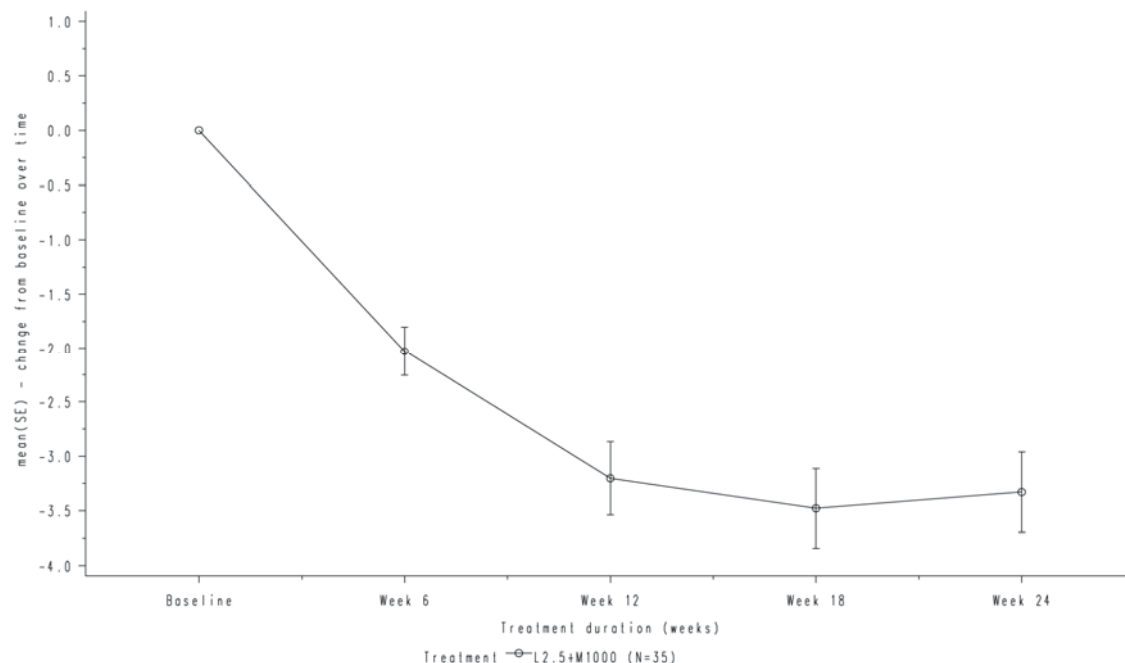


Source: CTR 1218.46, Figure 15.2.1.2.2.1

Reviewer's comment: This figure displaying the change in mean HbA1c by visit over time, designed by the applicant, emphasizes the effect of the combination therapy on the change in HbA1c. Overall, the maximal effect is observed at 12-18 weeks and maintained at 24 weeks.

Open-label arm: From baseline to Week 24, across visits, a decrease in HbA1c was seen with a maximum of -3.9% at Week 18 (observed cases). Figure 4 provides a graphical presentation of the change at each visit.

Figure 4: Change in unadjusted mean HbA1c (%) change from baseline over time - Open Label Arm



Prior OADs=No

Source: CTR 1218.46, Figure 15.2.1.2.2.2:2

6.1.5.2 Change from baseline in FPG - after 24 weeks of treatment

The change in FPG from baseline to the last on-treatment visit was analyzed similarly to the change in HbA1c from baseline, with the additional covariate of baseline FPG. Baseline FPG was defined as the last available FPG before the start of randomized study drug. The mean baseline FPG values was higher in the placebo arm (203 mg/dL) compared to the active treatment groups (ranging from 191 to 199 mg/dL).

The results of the primary analysis in the FAS population are summarized in Table 14. The sensitivity analyses using the PPS and the FPS-completers population showed similar differences between the treatment groups, with all p-values <0.05.

Table 14: Differences between adjusted means for the change in FPG (mg/dL) from baseline at Week 24 - FAS (LOCF)

Treatment group	Number of patients, N (%) ²	FPG baseline, mean (SD)	Change in FPG from baseline		Difference to Lina/Met combination		
			Mean (SD)	Adjusted ¹ mean (SE)	Adjusted ¹ mean (SE)	95% CI	p-value
Placebo	61 (8.3)	203.3 (51.5)	6.0 (55.8)	10.2 (5.26)			
Lina 2.5 + Met 500 bid	135 (18.4)	198.6 (60.2)	-34.5 (49.5)	-33.2 (3.54)			
Met 500 bid	136 (18.5)	190.6 (46.6)	-13.4 (52.5)	-15.8 (3.52)	-17.4 (4.99)	(-27.2, -7.6)	0.0005
Lina 5 qd	134 (18.3)	195.3 (50.2)	-8.0 (46.8)	-8.6 (3.55)	-24.6 (5.01)	(-34.4, -14.8)	<0.0001
Lina 2.5 + Met 1000 bid	136 (18.5)	195.6 (50.4)	-49.5 (46.4)	-49.4 (3.52)			
Met 1000 bid	132 (18.0)	190.6 (52.2)	-30.2 (42.9)	-32.2 (3.58)	-17.2 (5.02)	(-27.1, -7.3)	0.0006
Lina 5 qd	134 (18.3)	195.3 (50.2)	-8.0 (46.8)	-8.6 (3.55)	-40.8 (5.00)	(-50.6, -31.0)	<0.0001

Lina = linagliptin; Met = metformin

¹ Model includes continuous baseline HbA_{1c}, continuous baseline FPG, prior use of anti-diabetic drugs, and treatment.

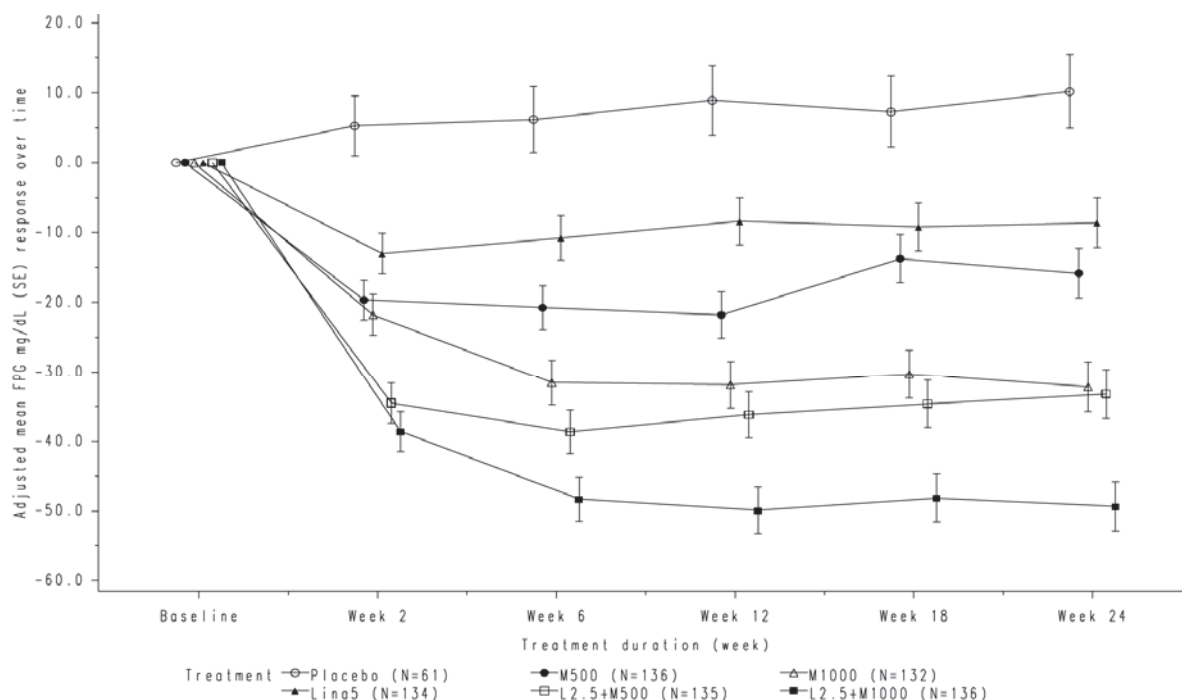
² Patients in the FAS with a baseline FPG value and at least one on-treatment FPG value.

Source: SCE, Table 3.2.1.2:1

6.1.5.3 Change in FPG from baseline by visit over time

Randomized arms: The mean change in FPG from baseline over time was analyzed, and from baseline to Week 24, at each visit, a greater reduction in the adjusted mean change in FPG were seen in the combination treatment arms compared to the individual metformin and linagliptin component arms, with all p-values <0.01 for each comparison. Figure 5 displays the change in adjusted mean FPG over time.

Figure 5: Change in adjusted mean FPG (mg/dL) from baseline over time - FAS (LOCF)



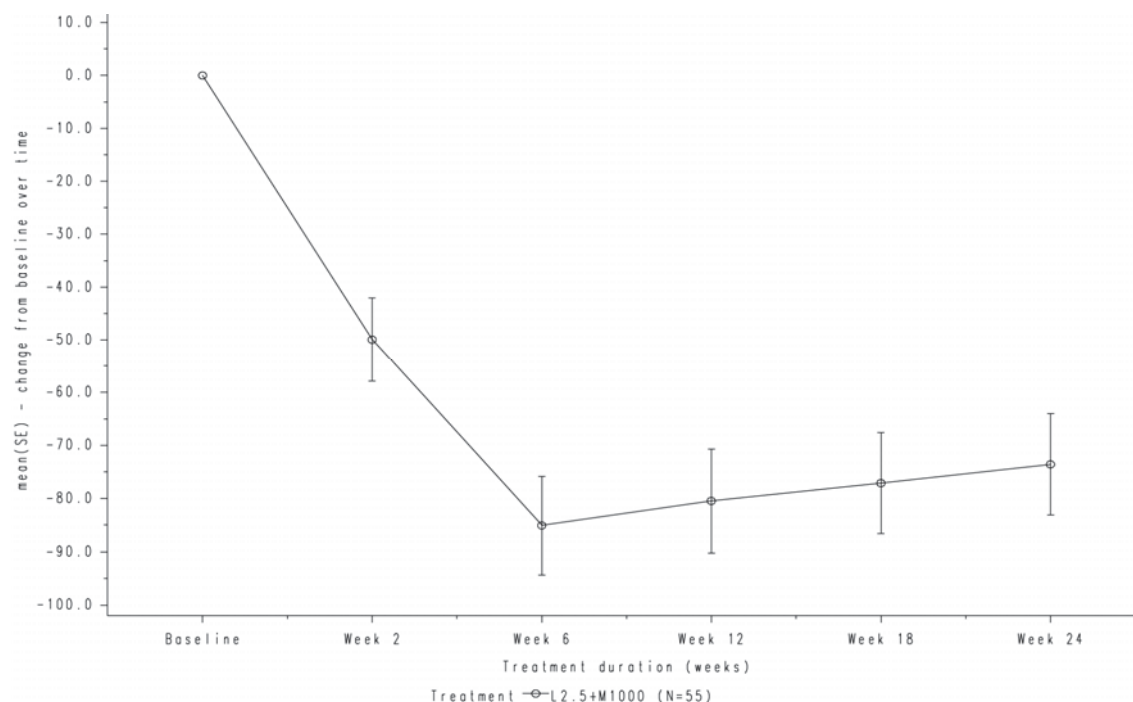
LS Mean $\pm$ SE, adjusted for baseline HbA1c, baseline FPG and prior OADs

Source: CTR, Figure 15.2.2.1.1:1

Reviewer's comment: Similar to figures for HbA1c change over time, the above figure displaying the change in mean FPG by visit over time, designed by the applicant, emphasizes the effect of the combination therapy on the change in FPG. Overall, the maximal effect is observed at about 6 weeks and somewhat maintained at 24 weeks.

Open arm: From baseline to Week 24, a decrease in FPG was seen with a maximal change from baseline observed at Week 6 (-85 mg/dL). Figure 6 provides a graphical presentation of the change at each visit.

Figure 6: Change in unadjusted mean FPG (mg/dL) change from baseline over time - Open Label Arm



Source: CTR 1218.46, Figure 15.2.2.1.2:1

6.1.5.4 Categorical efficacy response

The responder analysis was performed by determining the percentage of subjects who fulfilled the responder criteria (absolute and relative response) by treatment. For this analysis, missing values were imputed using the non-completers considered failure (NCF) approach, where missing data due to premature discontinuation of subject were considered failure. A logistic regression analysis with treatment as factor and continuous HbA1c as covariate was used to calculate the odds ratio of the study drug to the placebo.

The absolute efficacy response category evaluated the number of subjects reaching target HbA1c levels of <7.0% or 6.5% after 24 weeks of treatment. The relative response category evaluated the number of subjects who had their HbA1c levels lowered by 0.5% or more after 24 weeks of treatment.

A summary of number of subjects with categorical efficacy response is presented in Table 15. Overall, the proportions of subjects with at least 0.5% reduction in HbA1c were higher in the active treatment groups compared to the placebo. In both absolute and relative response categories, the odds of achieving a reduction in HbA1c was higher for subjects on combination therapy with linagliptin and metformin compared to monotherapy with either component. The odds ratio was highest when L2.5+M1000 was compared to L5, whereas the odds ratio for the

other comparisons were comparable. Table 15 presents the results of these categorical efficacy responses.

Table 15: Number of subjects with categorical response at Week 24 (NCF)

Response criterion	Met 0		Met 500 b.i.d.		Met 1000 b.i.d.	
	n ¹ (%)	N ²	n ¹ (%)	N ²	n ¹ (%)	N ²
HbA _{1c} <7.0%						
Lina 0						
HbA _{1c} <7.0%	7 (10.8)	65	27 (19.1)	141	43 (31.2)	138
Among patients with baseline HbA _{1c} ≥7.0%	7 (10.8)	65	26 (18.6)	140	42 (30.7)	137
Lina 5 q.d./ 2.5 b.i.d. ³						
HbA _{1c} <7.0%	14 (10.4)	135	42 (30.7)	137	76 (54.3)	140
Among patients with baseline HbA _{1c} ≥7.0%	14 (10.4)	135	41 (30.1)	136	74 (53.6)	138
HbA _{1c} <6.5%						
Lina 0						
HbA _{1c} <6.5%	2 (3.1)	65	7 (5.0)	141	17 (12.3)	138
Among patients with baseline HbA _{1c} ≥6.5%	2 (3.1)	65	7 (5.0)	141	17 (12.3)	138
Lina 5 q.d./ 2.5 b.i.d. ³						
HbA _{1c} <6.5%	5 (3.7)	135	18 (13.1)	137	38 (27.1)	140
Among patients with baseline HbA _{1c} ≥6.5%	5 (3.7)	135	18 (13.1)	137	38 (27.1)	140
HbA _{1c} reduction from baseline ≥0.5%						
Lina 0	19 (29.2)	65	65 (46.1)	141	91 (65.9)	138
Lina 5 q.d./ 2.5 b.i.d. ³	57 (42.2)	135	98 (71.5)	137	114 (81.4)	140

¹ Number of patients with a response

² Number of patients analysed

³ If combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

Source: CTR 1218.46, Table 11.4.1.2.3:1

6.1.5.5 Two-hour post-prandial glucose (2-hour PPG), measured after MTT

A meal tolerance test (MTT) was done in a subgroup of subjects at selected visits, and 2-hour postprandial glucose (2h-PPG) was determined 2 hours after the intake of a standardized meal. The change in 2-PPG from baseline to the last on-treatment visit was analyzed similarly to the change in HbA_{1c} from baseline, with the additional covariate of baseline 2-PPG, in a subgroup of subjects where adequate MTT results were available at the beginning and at the end of the randomized treatment period (missing values not imputed; MTT set).

Although the available results are provided in Table 16, it is hard to interpret these results as the number of subjects available for analysis was very small and was underpowered to show any difference. About 90% of subjects did not have valid MTT results at baseline and end of treatment, and were excluded from MTT set.

Table 16: Differences between adjusted means for 2h PPG (mg/dL) change from baseline at Week 24 - MTT set

Treatment group	Number of patients, N (%) ²	2h-PPG baseline, mean (SD)	Change in 2h-PPG from baseline		Difference to Lina/Met combination		
			Mean (SD)	Adjusted ¹ mean (SE)	Adjusted ¹ mean (SE)	95% CI	p-value
Placebo	6 (8.7)	254.67 (63.96)	-11.00 (68.70)	-35.37 (23.22)			
Lina 2.5 + Met 500 bid	10 (14.5)	325.10 (87.49)	-100.50 (73.86)	-86.04 (17.51)			
Met 500 bid	15 (21.7)	289.40 (72.35)	-75.93 (63.03)	-82.87 (14.39)	-3.17 (22.66)	(-48.49, 42.16)	0.8893
Lina 5 qd	12 (17.4)	298.17 (71.34)	-32.25 (67.57)	-35.26 (16.11)	-50.78 (23.84)	(-98.47, -3.09)	0.0373
Lina 2.5 + Met 1000 bid	12 (17.4)	334.08 (91.38)	-128.75 (85.63)	-109.18 (16.17)			
Met 1000 bid	14 (20.3)	287.64 (94.57)	-80.36 (77.26)	-87.18 (14.76)	-22.00 (22.10)	(-66.20, 22.20)	0.3234
Lina 5 qd	12 (17.4)	298.17 (71.34)	-32.25 (67.57)	-35.26 (16.11)	-73.92 (22.66)	(-119.25, -28.59)	0.0018

Lina = linagliptin; Met = metformin

¹ Model includes continuous baseline HbA_{1c}, continuous baseline 2h-PPG, prior use of anti-diabetic drugs, and treatment.

² Patients in the MTT set with a baseline 2h-PPG value and Week 24 2h-PPG value

Source: SCE, Table 3.2.1.3:1

6.1.5.6 Use of rescue therapy

The use of rescue therapy (SUs, TZDs, or insulin) was permitted in this trial if a subject had a confirmed glucose level >400 mg/dL or a fasting glucose of >240 mg/dL during the first 12 weeks of randomized treatment, and confirmed glucose level >400 mg/dL or a fasting glucose of >200 mg/dL during the remaining weeks of the randomized treatment.

As presented in Table 17, the proportion of subjects requiring rescue therapy was higher in the placebo group (29.2%) compared to the active treatment groups. The use of rescue therapy was lower in the L2.5+M1000, L2.5+M500, and M1000 arm at 4.3%, 7.3%, and 8% respectively.

Table 17: Number of subjects with rescue therapy - FAS (OC)

	Placebo	M500	M1000	Lina5	L2.5+M500	L2.5+M1000
Number of patients	65 (100.0)	141 (100.0)	138 (100.0)	135 (100.0)	137 (100.0)	140 (100.0)
Rescue medication [N (%)]						
N	65 (100.0)	141 (100.0)	138 (100.0)	135 (100.0)	137 (100.0)	140 (100.0)
Yes	19 (29.2)	19 (13.5)	11 (8.0)	15 (11.1)	10 (7.3)	6 (4.3)
No	46 (70.8)	122 (86.5)	127 (92.0)	120 (88.9)	127 (92.7)	134 (95.7)
Relative day						
N	19	19	11	15	10	6
Mean	54.7	91.5	81.5	84.7	105.7	63.5
SD	40.9	53.2	66.5	45.4	44.5	61.9
Min	6	5	3	11	15	7
Median	43.0	100.0	89.0	86.0	104.5	48.0
Max	157	177	181	155	171	168

Source: CTR 1218.46, Table 15.2.2.7:2

6.1.6 Other Endpoints - Change in body weight

The change from baseline in body weight at 24 weeks was tested using ANCOVA similar to the analysis of HbA1c, with the additional covariate of baseline body weight. The FAS (Observed Cases [OC]) was used for this analysis, where missing data were not replaced and values measured after rescue therapy were set to missing.

The results are summarized in Table 18. The highest difference among the treatment groups in the adjusted means of the change from baseline was the weight loss of 0.96 kg (95% CI -1.67, -0.24) observed with L2.5+M1000 compared to L5, which reached nominal significance (p=0.0086). Compared to M500 arm, L5+M500 arm showed an increase in body weight of 0.61 kg.

Table 18: Change in adjusted mean body weight (kg) from baseline at Week 24 - FAS (OC)

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	43	117	122
Baseline unadjusted mean (SD)	77.23 (18.07)	80.04 (18.17)	80.94 (18.08)
End of study adjusted mean (SE)	78.84 (0.43)	78.80 (0.26)	78.99 (0.26)
Change to end of study adjusted mean (SE)	-0.68 (0.43)	-0.71 (0.26)	-0.52 (0.26)
Lina 5 od/ Lina 2.5 bid*			
N	112	122	131
Baseline unadjusted mean (SD)	79.03 (16.87)	81.47 (18.96)	77.04 (15.70)
End of study adjusted mean (SE)	79.72 (0.27)	79.41 (0.26)	78.76 (0.25)
Change to end of study adjusted mean (SE)	0.21 (0.27)	-0.10 (0.26)	-0.75 (0.25)
Difference to Met component		0.61 (0.37)	-0.23 (0.36)
95% CI		(-0.11, 1.32)	(-0.93, 0.47)
p-value		0.0985	0.5183
Difference to Lina 5		-0.31 (0.37)	-0.96 (0.36)
95% CI		(-1.04, 0.42)	(-1.67, -0.24)
p-value		0.4034	0.0086

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
Model includes treatment, continuous baseline HbA1c, continuous baseline weight and prior OADs

Source: CTR 1218.46, Table 15.2.3.1:1

6.1.7 Subpopulations

The unadjusted means for the change in HbA1c after 24 weeks by subgroups based on demographic and baseline disease characteristics are presented in Table 19. The treatment effect was consistent across different subgroup variables.

Table 19: Change in unadjusted mean HbA1c from baseline by subgroups - FAS (LOCF)

	Placebo		Lina 5		Met 500		Met 1000		Lina 2.5 + Met 500		Lina 2.5 + Met 1000	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline HbA _{1c} [%]												
<7.5	4	0.30 (0.72)	4	0.43 (0.60)	6	-0.75 (0.64)	9	-0.21 (1.11)	5	-0.50 (0.58)	13	-1.02 (0.58)
7.5 to <8.0	14	0.11 (0.89)	32	-0.13 (0.71)	27	-0.45 (0.68)	37	-0.70 (0.65)	32	-0.90 (0.63)	23	-1.07 (0.55)
8.0 to <9.0	21	0.45 (1.49)	55	-0.31 (1.09)	57	-0.35 (0.98)	47	-0.98 (0.78)	49	-0.96 (0.93)	55	-1.51 (0.82)
≥9.0	26	-0.15 (1.03)	44	-0.88 (1.09)	51	-1.04 (1.21)	45	-1.47 (1.23)	51	-1.75 (1.02)	49	-2.02 (1.18)
Number of prior OADs												
0	32	-0.23 (0.94)	61	-0.69 (1.15)	69	-1.07 (0.96)	67	-1.35 (1.12)	65	-1.63 (1.02)	65	-1.84 (0.97)
1	33	0.47 (1.27)	74	-0.22 (0.92)	72	-0.22 (0.97)	71	-0.70 (0.77)	72	-0.86 (0.79)	75	-1.34 (0.93)
Region												
Africa	4	0.32 (0.33)	5	-1.32 (1.72)	7	-0.66 (1.28)	4	-2.20 (1.04)	7	-2.14 (1.33)	5	-2.18 (1.48)
Asia	23	0.23 (1.42)	40	-0.54 (1.11)	49	-0.77 (1.11)	45	-1.07 (1.07)	36	-1.23 (0.95)	44	-1.60 (1.16)
Europe	26	0.17 (0.89)	70	-0.35 (0.99)	62	-0.46 (0.98)	66	-0.96 (0.97)	70	-1.01 (0.88)	63	-1.49 (0.81)
N.America	2	0.95 (0.07)	7	-0.30 (0.41)	6	-0.28 (0.21)	7	-0.84 (1.03)	9	-1.19 (0.51)	10	-1.44 (0.45)
S. America	10	-0.47 (1.39)	13	-0.27 (1.07)	17	-0.99 (1.16)	16	-0.88 (0.87)	15	-1.78 (1.20)	18	-1.71 (1.11)
Race ¹												
Asian	23	0.23 (1.42)	42	-0.52 (1.09)	51	-0.74 (1.10)	46	-1.07 (1.06)	36	-1.23 (0.95)	47	-1.58 (1.13)
White	42	0.07 (1.02)	93	-0.39 (1.04)	90	-0.57 (1.03)	91	-0.99 (0.99)	98	-1.24 (1.00)	92	-1.58 (0.90)
Ethnicity												
Not Hisp/L	55	0.23 (1.10)	121	-0.45 (1.05)	122	-0.58 (1.02)	120	-1.05 (1.03)	121	-1.16 (0.94)	122	-1.55 (0.96)
Hisp/L	10	-0.47 (1.39)	13	-0.27 (1.07)	19	-0.98 (1.19)	17	-0.86 (0.85)	16	-1.73 (1.18)	18	-1.71 (1.11)

Baseline HbA _{1c} [%] and number of prior OADs												
<8.5 - 0	13	-0.08 (0.83)	32	-0.16 (1.00)	32	-0.86 (0.75)	33	-0.86 (0.78)	27	-1.40 (0.83)	35	-1.25 (0.61)
<8.5 - 1	18	0.64 (1.49)	34	-0.04 (0.76)	36	-0.11 (0.73)	41	-0.56 (0.67)	36	-0.48 (0.69)	31	-1.13 (0.75)
≥8.5 - 0	19	-0.33 (1.02)	29	-1.28 (1.02)	37	-1.25 (1.09)	34	-1.82 (1.21)	38	-1.79 (1.12)	30	-2.53 (0.85)
≥8.5 - 1	15	0.27 (0.96)	40	-0.38 (1.01)	36	-0.33 (1.15)	30	-0.90 (0.86)	36	-1.23 (0.71)	44	-1.49 (1.03)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

Note that descriptive statistics were not performed for the subgroups country, BMI, time since diagnosis of diabetes, metabolic syndrome at screening, age, and gender.

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

¹ There were in total 4 Black patients (1 patient in the met 1000 group, 2 patients in the lina 2.5 + met 500 group, and 1 patient in the lina 2.5 + met 1000 group) and 1 Hawaiian/Pacific Isle patient in the lina 2.5 + met 500 group

Source: CTR 1218.46, Table 11.4.1.1.2:1

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The available dose range for metformin is 500 mg, 850 mg, and 1000 mg, to be given twice daily. Linagliptin is given at 5 mg dose once daily. Since metformin is to be given twice daily, the linagliptin dose was split into 2.5 mg, to be given twice daily for the FDC. A PK/PD bridging trial 1218.4 in health volunteers demonstrated that linagliptin given 2.5 mg BID versus linagliptin 5 mg QD are bioequivalent with regard to total exposure (steady state AUC) and DPP-4 inhibition. This was reviewed in the linagliptin NDA 201280.

Trial 1218.17 was also reviewed in linagliptin NDA 201280 by Dr. Dunn. Briefly, this was a randomized, double-blind, placebo-controlled parallel group efficacy and safety trial of linagliptin 5 mg QD over 24 weeks in subjects with T2DM and insufficient glycemic control despite metformin therapy, testing linagliptin as an add-on therapy to subjects who are on metformin therapy.

In this FDC submission, the applicant submitted efficacy results for subset of subjects with metformin background doses of 850 mg BID and 1000 mg BID in trial 1218.17 in support of metformin 850 mg BID dose for the FDC (Table 20), since the factorial trial 1218.46 only tested the combination of linagliptin 2.5 mg with metformin 500 mg and 1000 mg BID. This subgroup analysis demonstrated that treatment with L5+M850 and L5+M1000 significantly reduced the adjusted mean change in HbA_{1c} from baseline to Week 24 when compared to placebo+M850 and placebo+M1000 respectively. The baseline HbA_{1c} values were comparable between the groups. This result is consistent with the results of trial 1218.46, where the combination therapy was effective, and provides supportive data for the combination dose of linagliptin 5 mg/metformin 850 mg.

Table 20: Differences between adjusted means for HbA1c change from baseline at Week 24 in trial 1218.17 - Metformin background doses - FAS (LOCF)

Treatment group	Number of patients, N (%)	HbA _{1c} baseline, mean (SD)	Change in HbA _{1c} from baseline		Difference to Lina/Met combination		
			Mean (SD)	Adjusted ¹ mean (SE)	Adjusted ¹ mean (SE)	95% CI	p-value
Metformin background dose: 850 mg BID							
Lina 5 qd + Met 850 bid	156 (30.4)	8.01 (0.80)	-0.61 (0.71)	-0.56 (0.07)	-0.70 (0.15)	(-1.00, -0.39)	<0.0001
Placebo + Met 850 bid	35 (20.0)	8.11 (0.92)	0.06 (1.05)	0.13 (0.14)			
Metformin background dose: 1000 mg BID							
Lina 5 qd + Met 1000 bid	66 (12.9)	7.90 (0.88)	-0.34 (0.82)	-0.36 (0.10)	-0.67 (0.19)	(-1.05, -0.29)	0.0005
Placebo + Met 1000 bid	26 (14.9)	7.88 (0.82)	0.33 (1.02)	0.31 (0.16)			
Metformin background dose: Other							
Lina 5 qd + Metformin	291 (56.7)	8.18 (0.88)	-0.58 (0.88)	-0.49 (0.05)	-0.60 (0.09)	(-0.78, -0.42)	<0.0001
Placebo + Metformin	114 (65.1)	8.03 (0.88)	0.06 (0.99)	0.11 (0.08)			

Lina = linagliptin

¹ Model includes continuous baseline HbA_{1c}, number of anti-diabetic drugs, dose, treatment and treatment*dose.

Source: SCE, Table 3.3.1.1:1

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects - Trial 1218.52

The results of Trial 1218.46 (24 weeks duration) combined with extension Trial 1218.52 (interim analysis data, with cut-off date of June 8, 2010) provide the evidence of long term efficacy and safety for the combination of linagliptin 2.5 mg + metformin (500 or 1000 mg). For the extension Trial 1218.52, only those subjects participating in the double-blind Trial 1218.46 who took at least one dose of study drug in Trial 1218.52 were included in the analysis (Treated Set).

6.1.9.1 Demographics

Overall, the baseline demographic data and disease characteristics were comparable between treatment groups (Table 21 and Table 22).

Table 21: Demographic data by randomized treatment group – Treated Set

	Met 1000	lina 2.5 + met 500	lina 2.5 + met 1000	Total
Total patients, n (%)	170 (100.0)	225 (100.0)	171 (100.0)	566 (100.0)
Age, mean (SD) [years]	55.6 (10.7)	56.0 (10.7)	55.7 (10.8)	55.8 (10.7)
Age by category, n (%)				
<65	132 (77.6)	176 (78.2)	135 (78.9)	443 (78.3)
65-74	35 (20.6)	38 (16.9)	32 (18.7)	105 (18.6)
≥75	3 (1.8)	11 (4.9)	4 (2.3)	18 (3.2)
Male sex, n (%)	93 (54.7)	120 (53.3)	97 (56.7)	310 (54.8)
Race, n (%)				
Asian	62 (36.5)	69 (30.7)	62 (36.3)	193 (34.1)
Black/African Amer.	1 (0.6)	2 (0.9)	1 (0.6)	4 (0.7)
White	107 (62.9)	154 (68.4)	108 (63.2)	369 (65.2)
Ethnicity, n (%)				
Not Hispanic/Latino	156 (91.8)	203 (90.2)	160 (93.6)	519 (91.7)
Hispanic/Latino	13 (7.6)	22 (9.8)	10 (5.8)	45 (8.0)
Missing	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Weight [kg], mean (SD)	81.1 (18.9)	79.2 (18.8)	78.6 (16.9)	79.6 (18.3)
Weight [kg] by category, n (%)				
≤70	59 (34.7)	77 (34.2)	58 (33.9)	194 (34.3)
>70 to 80	25 (14.7)	49 (21.8)	39 (22.8)	113 (20.0)
>80 to 90	29 (17.1)	38 (16.9)	37 (21.6)	104 (18.4)
>90	57 (33.5)	60 (26.7)	37 (21.6)	154 (27.2)
Missing	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
BMI [kg/m ²], mean (SD)	29.33 (5.22)	29.06 (4.95)	28.64 (4.79)	29.01 (4.98)
BMI [kg/m ²] by category, n (%)				
<25	39 (22.9)	46 (20.4)	40 (23.4)	125 (22.1)
25 to <30	58 (34.1)	90 (40.0)	70 (40.9)	218 (38.5)
≥30	73 (42.9)	88 (39.1)	61 (35.7)	222 (39.2)
Missing	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
eGFR (MDRD staging)				
[mL/min] by category, n (%) ¹				
≥90	96 (56.5)	125 (55.6)	85 (49.7)	306 (54.1)
60 to <90	64 (37.6)	95 (42.2)	73 (42.7)	232 (41.0)
30 to <60	4 (2.4)	4 (1.8)	10 (5.8)	18 (3.2)
Missing ²	6 (3.5)	1 (0.4)	3 (1.8)	10 (1.8)

¹ The degree of renal impairment was based on eGFR as calculated by the MDRD formula:
none ≥90 mL/min; mild 60 to <90 mL/min; moderate 30 to <60 mL/min; severe <30 mL/min

² Missing samples were either non-evaluable or were beyond their viability date.

Source: CTR 1218.52, Table 11.2.1:1

Table 22: Baseline efficacy variables – Treated Set

	Met 1000	lina 2.5 + met 500	lina 2.5 + met 1000	Total
Number (%) of treated patients	170 (100.0)	225 (100.0)	171 (100.0)	566 (100.0)
HbA _{1c} [%]				
Number of patients	165	224	170	559
Mean (SD)	7.48 (0.99)	7.64 (1.04)	7.35 (1.12)	7.50 (1.06)
By category [%], n (%)				
<7.0	53 (31.2)	58 (25.8)	76 (44.4)	187 (33.0)
7.0 to <8.0	66 (38.8)	89 (39.6)	49 (28.7)	204 (36.0)
8.0 to <9.0	29 (17.1)	55 (24.4)	28 (16.4)	112 (19.8)
≥9.0	17 (10.0)	22 (9.8)	17 (9.9)	56 (9.9)
Missing	5 (2.9)	1 (0.4)	1 (0.6)	7 (1.2)
FPG [mg/mL]				
Number of patients	164	215	165	544
Mean (SD)	156.6 (39.19)	167.1 (44.63)	153.7 (37.13)	159.9 (41.21)
By category [mg/dL], n (%)				
<126	34 (20.0)	28 (12.4)	34 (19.9)	96 (17.0)
126 to <140	30 (17.6)	33 (14.7)	40 (23.4)	103 (18.2)
140 to <200	78 (45.9)	112 (49.8)	74 (43.3)	264 (46.6)
≥200	22 (12.9)	42 (18.7)	17 (9.9)	81 (14.3)
Missing	6 (3.5)	10 (4.4)	6 (3.5)	22 (3.9)
Duration of diabetes (years), n (%)				
≤1	65 (38.2)	94 (41.8)	71 (41.5)	230 (40.6)
>1 to 5	69 (40.6)	77 (34.2)	67 (39.2)	213 (37.6)
>5	36 (21.2)	54 (24.0)	33 (19.3)	123 (21.7)
Number of antidiabetic treatments, n (%)				
0	170 (99.4)	224 (99.6)	171 (100.0)	565 (99.8)
1	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

Source: CTR 1218.52, Table 11.2.4.1:1

6.1.9.2 Subject Disposition

A total of 567 subjects were enrolled in this extension trial (screened set); of these, 566 subjects were treated. Of 566 treated subjects, 333 (58.7%) were continuing the treatment that was assigned in trial 1218.46, and the remainder 233 subjects were switched and re-randomized to treatments in this extension trial. At the cut-off date for this first interim analysis, most subjects were continuing the trial (530 subjects, 93.6%). Of 36 subjects who discontinued the trial, the most common reason was an AE (16 subjects, 2.8%)

The treated set (TS) are all subjects in the screened set who received at least one dose of study drug in the extension trial (N=566). The switched set (SWS) is a subset of the TS who switched treatments between 1218.46 and 1218.52 (N=233), the non-switched set (NONS) are all subjects who continued to take the same treatments in this extension trial 1218.52 that they took in previous trial 1218.46. The proportion of subjects who switched treatments between the trials

was higher for the L2.5+M500 arm (49.8%) compared to the other two arms, which is most likely due to the imbalance in the randomization scheme into the three treatment arms (Figure 2). Table 23 provides the subject distribution in treatment groups.

Table 23: Datasets in trial 1218.46

	Met 1000 N (%)	lina 2.5 + met 500 N (%)	lina 2.5 + met 1000 N (%)	Total N (%)
Screened set	171	225	171	567
Randomised set	171 (100.0)	225 (100.0)	171 (100.0)	567 (100.0)
Treated set (TS)	170 (99.4)	225 (100.0)	171 (100.0)	566 (99.8)
Excluded from the TS	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Switched set (SWS)	61 (35.7)	112 (49.8)	60 (35.1)	233 (41.1)
Non-switched set (NONS)	109 (63.7)	113 (50.2)	111 (64.9)	333 (58.7)

Source: CTR 1218.52, Table 11.1:1

6.1.9.3 Analysis of Secondary Endpoints

There was no primary efficacy endpoint in this trial, and the primary safety endpoints are discussed in section 7, Review of Safety. The secondary endpoints that is applicable here is HbA1c and FPG change over time (up to 54 weeks).

All endpoints were analyzed using the TS. The baseline for the first interim analysis was Visit 1 of the extension trial. As mentioned previously, trial 1218.52 was an extension trial for 54 weeks, but not all data were available at the interim analysis provided by the applicant. This first interim analysis did not have enough subjects with data beyond Week 6 to assess secondary efficacy endpoints.

For analysis of HbA1c, of 559 subjects with baseline data, 446 subjects had data at Week 6, 167 at Week 18, 45 at Week 30, 6 at Week 42, and none at Week 54. The largest reduction in HbA1c from baseline to Week 6 was seen in L2.5+M1000 (-0.3%) and L2.5+M500 (-0.2%) than in the M1000 group (-0.1) in the TS. Similar pattern was reported at Week 18 with currently available data. For subjects who stayed on the same treatment in trial 1218.52 as they were in 1218.46 (NONS), the mean change in HbA1c from baseline to Week 6 was comparable in all treatment groups.

For analysis of FPG, of 544 subjects with baseline data, 488 subjects had data at Week 2, 390 at Week 6, 138 at Week 18, 31 at Week 30, and 2 at Week 42. The largest reduction in FPG from baseline to Week 6 was observed in L2.5+M500 (-14 mg/dL) and L2.5+M1000 (-13 mg/dL) than the M1000 group (-5 mg/dL). Similarly, for subjects in the NONS, the mean change in FPG from baseline to Week 2 was larger in both combination therapy treatment groups than in the met 1000 group.

Reviewer's comment: This extension trial was primarily designed to assess safety, and the efficacy data are only descriptive without any hypothesis testing. The interim data presented by the applicant were insufficient for adequate interpretation; there were too few subjects with data beyond 6 weeks of treatment period in the extension trial to describe the long term efficacy for combined linagliptin and metformin therapy.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

Of the clinical study reports submitted, only trials 1218.46 and 1218.52 were not previously reviewed and are reviewed here. Pooled safety data of all the six phase 1 clinical pharmacology trials were reviewed, and pooled safety data of three 12 and 24-week metformin-controlled trials were reviewed to compare the safety profile of L+M combined therapy compared to metformin monotherapy.

A total of 3084 subjects with T2DM were exposed to the coadministration of linagliptin and metformin across Phase 2 and 3 trials, providing a total of 3006 patient-years of exposure. The most frequently reported adverse events (AEs) for L+M therapy were hyperglycemia (12.1%), hyperglycemia (11.1%), and nasopharyngitis (9.2%).

In trial 1218.46, a total of 791 subjects were randomized to placebo (N=72), L5 (N=142), metformin 500 or 1000 monotherapy (N=291), and either L2.5+M500 or L2.5+M1000 combination therapy (N=286). One death due to myocardial infarction (MI) occurred in a 66 year old subject two days after receiving randomized treatment of metformin 1000 mg; he had a history of hypertension, abnormal ECG, and hypertriglyceridemia. The frequency of non-fatal serious adverse events (SAEs) was low overall, and no particular trend was observed. Diarrhea and headache were most commonly reported AEs that led to trial discontinuation, and was only reported in the treatment arms with metformin therapy.

An interim analysis for trial 1218.52 was provided, as it is still ongoing, and the mean duration of exposure was about 3 months across three treatment arms. Overall, about 80% of subjects have completed 6 weeks of trial, but only 30% of subjects completed 18 weeks, not providing adequate data to evaluate the intended long-term safety. One death occurred due to a road traffic accident. No trend was observed in the non-fatal SAEs, and the most frequent AE that led to trial discontinuation was decreased GFR to <60 mL/min, reported in each arms treated with coadministration of linagliptin and metformin.

Due to previous experience with other DPP-4 inhibitors, adverse events of special interest included hypersensitivity reaction, renal events, hepatic events, severe cutaneous adverse

reactions, and pancreatitis. In trial 1218.46, similar incidence of hepatic events occurred across active treatment arms in trial (mostly reporting increased ALT), and one periorbital edema was reported in the linagliptin monotherapy arm. In trial 1218.52, more hepatic events were reported in M1000 arm compared to the L+M arms, mostly related to increased liver aminotransferases. In both 1218.46 and 1218.52, there were no reports of pre-specified renal events, severe cutaneous skin lesions, or pancreatitis.

The overall hypoglycemia incidence was low in trial 1218.46, and was most frequently reported in M1000 and L2.5+M500 arms. No hypoglycemia was reported in the L2.5+M1000 arm. Most reported a single episode of hypoglycemia, and only one severe hypoglycemic episode requiring assistance was reported in the M1000 arm. In trial 1218.52, a higher incidence of hypoglycemia was observed in the coadministration arms compared to metformin monotherapy at the time of interim analysis.

In trial 1218.46, a higher incidence of diarrhea was observed in the L+M arms compared to its respective monotherapy arms. A higher incidence of nasopharyngitis was observed in the L+M arms compared to respective metformin monotherapy arms. GI disorders increased with increasing dose of metformin in both metformin monotherapy and L+M arms, which is not surprising. A higher incidence of nasopharyngitis was observed in the L+M arms and linagliptin monotherapy arm, compared to the metformin monotherapy and placebo arms. When the safety data are pooled across the metformin dose, nasopharyngitis (6.3%) and diarrhea (6.3%) were most frequently seen in the L+M arm, and metformin monotherapy arm had the highest incidence of hypoglycemia.

The pooled safety data from 12 and 24-week metformin monotherapy-controlled trials (which also included 1218.46, referred to as SEA-2) was reviewed to compare the safety profile of L+M compared to metformin monotherapy regardless of metformin dose. The following AEs were observed with higher frequency in the pooled L+M arm compared to the pooled metformin arm: diarrhea, nasopharyngitis, arthralgia, and back pain. Hyperglycemia and hypoglycemia were observed more frequently in the pooled metformin arm.

Although some small shifts in the laboratory parameters and vital signs were observed throughout the treatment period, no clinically significant changes or emerging trends in the laboratory parameters or vital signs were observed with the coadministration of linagliptin and metformin.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Of all the clinical study reports submitted, only 1218.46 and 1218.52 were not previously reviewed, and these were the trials that were reviewed for deaths and other SAEs, as well as changes in the laboratory parameters and vital sign. In order to assess the overall safety of the

combination L+M therapy in a larger patient population, pooled safety data were assessed. Different pooled data used in the safety evaluation are described in section 7.1.3, Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.

The Treated Sets (TS) were used to evaluate safety. The TS consisted of all subjects who received at least one dose of study drug.

For safety analysis of 1218.46, two approaches were used to evaluate safety. First, by assessing any differences between six treatment groups. Second, by pooling treatment groups without regard to the metformin dose (e.g., placebo, linagliptin, metformin, and L+M).

For trial 1218.52, death, other serious, and discontinuations due to AE represent both TS and SWS. For common AEs, only TS is presented here, since SWS comprised a small number of subjects; safety issues in SWS were noted if there was a significant finding in the SWS that differed from TS. Although AEs are discussed for trial 1218.52, laboratory parameters or vital signs are not discussed in this review, since only 30% of subjects had data beyond 6 weeks.

Data from the 4-Month Safety Update (4MSU) were included to update reported deaths. Data from 4MSU were reviewed and presented when there were notable findings.

Cardiac disorders occurred infrequently throughout the L+M combination therapy. Although the applicant continued to adjudicate MACE events throughout their linagliptin and metformin FDC clinical development, cardiovascular AEs will not be discussed in detail unless there is a notable finding since the overall cardiovascular risk with linagliptin was evaluated under the linagliptin NDA 201-280.

7.1.2 Categorization of Adverse Events

All AEs in the initial NDA were coded using MedDRA version 13.0. The 4MSU were coded using MedDRA version 13.1, but the difference in coding version were minor and did not appear to affect the overall safety analysis.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The following pooled data and analysis are presented here under relevant sections throughout the review of safety:

- SAF-1 provide a large, full safety database of T2DM subjects treated with L+M therapy in all Phase 2/3 trials, regardless of dose or exposure. Trials included here are 1218.6, 1218.17, 1218.18, 1218.20, 1218.40, 1218.46, and 1218.52.
- SEA-2 provides an analysis of the largest study pooling of controlled exposure to L+M versus placebo+M to identify side effects. SEA-2 included two Phase 3 trials with >24

weeks of exposure (1218.17 and 1218.46) and one Phase 2 trial with >12 weeks of exposure (1218.6).

- SAF-8 provided an integrated safety profile for all 354 healthy subjects who received the linagliptin/metformin FDC or coadministration of linagliptin + metformin during six single-dose Phase 1 pharmacology trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

SAF-1:

A total of 3084 subjects with T2DM were exposed to the co-administration with linagliptin and metformin across all Phase 2 and Phase 3 trials. The mean exposure to L+M regardless of dose was 356 days (about 51 weeks), with 83.8% of subjects completing at least 24 weeks of L+M therapy. The combined Phase 2/3 trials resulted in a total of 3006.2 patient-years of exposure to coadministration of L+M. This is an adequate clinical exposure to evaluate the coadministration of linagliptin and metformin.

Trial 1218.46:

The number of subjects exposed is adequate to assess the relative safety of co-administration of linagliptin with metformin compared to monotherapy with either linagliptin or metformin or placebo. A total of 791 subjects were randomized 1(placebo):2:2:2:2; 72 subjects to placebo, 142 subjects to L5, 291 subjects to metformin monotherapy (either 500 or 1000 mg), and 286 subjects to the combination therapy (either L2.5+M500 or L2.5+M1000). Table 24 summarizes the overall exposure for randomized treatment arms in trial 1218.46.

Table 24: 1218.46 - Exposure to randomized treatment by combination and monotherapy

	Pbo	Lina 5 mg	Met 500 mg	Met 1000 mg	Lina + Met 2.5 + 500mg	Lina + Met 2.5 + 1000mg
Number of patients, N	72	142	144	147	143	143
Exposure categories N (%)						
≥1 day	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)
≥2 weeks	69 (95.8)	141 (99.3)	141 (97.9)	145 (98.6)	140 (97.9)	143 (100.0)
≥4 weeks	66 (91.7)	139 (97.9)	140 (97.2)	141 (95.9)	137 (95.8)	142 (99.3)
≥12 weeks	60 (83.3)	129 (90.8)	136 (94.4)	134 (91.2)	132 (92.3)	135 (94.4)
≥24 weeks	47 (65.3)	111 (78.2)	119 (82.6)	114 (77.6)	116 (81.1)	119 (83.2)
Duration of treatment exposure [days]						
Mean (±SD)	144 (54.1)	158 (38.7)	162 (33.6)	157 (41.4)	159 (39.6)	162 (30.3)
Median	169	170	169	169	169	169
Min, Max	2 - 183	7 - 191	3 - 189	1 - 188	3 - 188	16 - 189
Patient-years	28.3	61.4	63.8	63.2	62.2	63.6

Source: SCS, Table 1.2.1:2

In the open-label arm, the mean exposure was 156.3 days, and a large proportion of subjects (69.7%) completed >24 weeks of the open-label treatment period.

Trial 1218.52:

At the time of the interim analysis, the mean duration of exposure was about 3 months across the three treatment arms. No subject had completed 54 weeks of treatment. Overall, about 80% of subjects in each treatment group had been treated for at least 6 weeks, but only about 30% of subjects had been treated for at least 18 weeks. At this interim analysis, there are not enough data with subjects who completed a significant portion of this extension trial to adequately evaluate the long-term safety.

Table 25: 1218.52 - Overall Exposure by randomized treatment

	Metformin	lina 2.5 + met 500	lina 2.5 + met 1000
Number of patients treated, n (%)	170 (100.0)	225 (100.0)	171 (100.0)
Exposure categories [weeks], n (%)			
0 to 2 weeks	1 (0.6)	2 (0.9)	4 (2.3)
>2 to 6 weeks	28 (16.5)	37 (16.4)	28 (16.4)
>6 to 18 weeks	81 (47.6)	110 (48.9)	83 (48.5)
>18 to 30 weeks	43 (25.3)	56 (24.9)	39 (22.8)
>30 to 42 weeks	16 (9.4)	20 (8.9)	14 (8.2)
>42 to 54 weeks	1 (0.6)	0 (0.0)	3 (1.8)
Exposure [days]			
Mean (SD)	109 (69)	105 (63)	107 (69)
Median	101	98	95
Sum [patient years]	50.7	64.9	50.2

Source: 1218.52 CTR, Table 12.1:1

7.2.2 Explorations for Dose Response

The applicant studied two different dose combinations for the proposed FDC with different metformin dose, linagliptin 2.5 mg with either metformin 500 mg or 1000 mg, to be given twice daily. Exposure to this different combination was detailed in the section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Population.

7.2.3 Special Animal and/or In Vitro Testing

A discussion of the relevant animal data can be found in section 4.3 Preclinical Pharmacology/Toxicology.

7.2.4 Routine Clinical Testing

The applicant obtained laboratory test, vital signs, and ECGs at appropriate time points during the treatment period in 1218.46 and 1218.52.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see section 4.4 Clinical Pharmacology of this review, and Dr. Khurana's review for full details. Also refer to the linagliptin (NDA 201-280) product labels for more information, including drug-drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please refer to section 2.4 Important Safety Issues With Consideration to Related Drugs for a list of the labeled safety concerns with linagliptin and metformin. There are two other approved DPP-4 inhibitors, saxagliptin (NDA 22-350) and sitagliptin (NDA 21-995), and their prescribing information is similar to linagliptin.

7.3 Major Safety Results

7.3.1 Deaths

Trial 1218.46:

There was one death due to myocardial infarction (MI) in a subject two days after receiving randomized treatment of metformin 1000 mg. A brief narrative is provided here:

Subject 49471 was a 66 year old Asian (Indian) male subject with T2DM, who started randomized study drug on (b) (6). His medical history included hypertension, and concomitant medications included olmesartan, amlodipine, pregabalin, aspirin (due to abnormal ECG), and atorvastatin (due to high triglycerides). He did not have a history of hypercholesterolemia or nephropathy. No changes in ECG were seen compared to the baseline. He only took the morning and evening dose of study drug on (b) (6) and did not take any further study drug since he did not feel well and thought that may be due to the study drug. On (b) (6), he died due to MI. No treatment was given, and an autopsy was not performed.

In addition, one subject died during the washout period from cardiogenic shock due to inferior wall infarction. This subject had a number of past significant medical history including previous anterior wall infarction with pulmonary edema. He did not receive either placebo run-in nor double-blind study drug.

No deaths were reported in the open-label arm.

Trial 1218.52:

One death occurred during the treatment period due to a road traffic accident. A brief narrative is provided here:

Subject 48949 was a 66-year old male with history of T2DM for more than 5 years, and was in the extension trial for 71 days when a fatal road traffic accident occurred. His past history included hypertension and hyperlipidemia for which he was being treated with

telmisartan and simvastatin respectively. He had received linagliptin 2.5 + metformin 1000 mg BID in 1218.46 and continued the same treatment in this extension trial.

4MSU:

Five additional deaths were reported since this NDA submission, which are summarized in Table 26. No particular trend in deaths were observed here.

Table 26: Listing of subjects who received coadministration of linagliptin and metformin and died due to AE during the randomized treatment period

Patient	Trial	Age/Gender	Study Drug	Fatal AE(s)	Treatment start date	AE onset date
20714	1218.20	76/M	L5+M	Bronchial carcinoma	Oct 20, 2008	(b) (4)
28314	1218.20	72/M	L5+M	Aortic aneurysm	Oct 21, 2008	
94336	1218.40	53/M	L5+M+SU	Sudden cardiac death	Apr 23, 2009	
96434	1218.40	59/M	L5+M+SU	Acute myocardial infarction	Mar 25, 2009	
48735	1218.52	60/F	L2.5+M	Road traffic accident, cardiac disorder	Oct 5, 2009	

Source: 4MSU, Table 2.1.2:1

7.3.2 Nonfatal Serious Adverse Events

Trial 1218.46:

The number of subjects reporting non-fatal SAEs were low overall and listed in Table 27: one subject in the placebo arm (1.4%), 3 subjects in the lina 5 arm (2.1%), 3 subjects in the met 500 arm (2.1%), 6 subjects in the met 1000 arm (4.1%), 2 subjects in the lina 2.5 + met 500 arm (1.4%), and 2 subjects in the lina 2.5 + met 1000 arm (1.4%). Of these, five subjects discontinued from the trial due to SAEs (Table 29).

The most frequently reported SAEs were cardiac disorders. All of the subjects who experienced cardiac-related SAEs had underlying cardiovascular disease. A complete evaluation of cardiovascular safety with linagliptin was conducted under linagliptin NDA 201280, where a meta-analysis showed that linagliptin was not associated with increased cardiovascular risk.

Table 27: 1218.46 - Listing of Nonfatal SAEs by Treatment Arm

Treatment arm	Subject ID	Age/Gender	Preferred Term	Onset Day	Duration (days)	SAE criteria	Outcome
Placebo	49021	79/F	Bradycardia	21	7	HO	Recovered
Lina 5	46913	58/M	Angina unstable	85	8	HO	Recovered
			Left ventricular failure	86	7	DS	Sequelae
			Myocardial infarction	20	31	OT	Sequelae
			Hypertension	85	1	HO	Recovered
	46493	69/F	Breast cancer stage 3	126	11	HO	Recovered
	49565	61/M	Myocardial ischemia	1	87	HO	Recovered
Met 500	49891	46/M	Thrombocytopenia	59	12	HO	Recovered
			Malaria	59	12	HO	Recovered
			Plasmodium falciparum infection	59	12	HO	Recovered
			Urinary tract infection	62	150*	HO	Not recovered
			Hematuria	87	3	HO	Recovered
	46451	52/M	Hyperglycemia	66	8	HO	Recovered
	48156	48/M	Bile duct cancer	160	57*	HO	Not recovered
Met 1000	49742	52/M	Hemorrhoids	17	2	HO, OT	Recovered
	48383	57/M	Erysipelas	95	28	HO	Recovered
	49840	73/M	Femoral neck fracture	41	49	HO	Recovered
	48198	53/M	Rotator cuff syndrome	118	327*	HO	Not recovered
	47008	50/F	Nephrolithiasis	84	5	HO	Recovered
			Renal colic	84	5	HO	Recovered
Lina 2.5 + Met 500	47062	49/F	Primary hyperparathyroidism	15	78	HO	Recovered
	47044	62/F	Femur fracture	141	98*	HO	Not recovered
Lina 2.5 + Met 1000	46526	69/M	Angina pectoris	36	11	HO	Recovered
			Cardiac failure congestive	36	68*	HO	Not recovered
			Myocardial ischemia	36	72*	HO	Not recovered
	47577	61/M	Hodgkin's disease	103	229*	OT	Not recovered

Source: CTR 1218.46, Table 15.4.2.1:1

*censored

SAE=serious adverse event; HO=hospitalization; LT=life threatening; DS=disability; OT=other important medical event

In the open-label arm, one subject reported an SAE of induced abortion after becoming pregnant at about 5.5 months after receiving the study drug (linagliptin 2.5 mg + metformin 1000 mg BID).

Trial 1218.52:

A total of 8 subjects reported non-fatal SAEs, which included 2 subjects on M1000 (1.2%), 4 subjects on L2.5+M500 (1.8%), and 2 subjects on L2.5+M1000 (1.2%). The SAEs in two subjects led to study drug discontinuation, cerebrovascular accident in the M1000 arm and severe anemia (which was related to colon cancer) in the L2.5+M500 arm. Similar to trial 1218.46, the

most frequently reported non-fatal SAEs were cardiac disorders, reported in three subjects; the past medical history in all three subjects was significant for underlying cardiac disease.

Table 28: 1218.52 - Listing of Nonfatal SAEs by Treatment Arm

Treatment arm	Subject ID	Age/Gender	Preferred Term	Onset Day	Duration (days)	SAE criteria	Outcome
Met 1000	46460	59/F	Atrial fibrillation	46	11	HO	Recovered
	49819	72/M	Cerebrovascular accident	55	31	HO, LT	Sequelae
Lina 2.5 + Met 500	46041	56/M	Joint dislocation	87	81	HO	Recovered
	47571	65/F	Anemia	106	29	HO	Recovered
			Colon cancer	121	123*	HO	Not recovered
	48324	32/F	Cataract	109	38	HO	Recovered
	49521	57/M	Ischemic stroke	157	12	HO	Sequelae
Lina 2.5 + Met 1000	47539	72/M	Coronary artery disease	135	37	HO	Recovered
	48980	75/M	Atrial flutter	9	42	HO	Not recovered

*censored; HO=hospitalization; LT=life-threatening

Source: 1218.52 CTR, Table 12.3.2:2

7.3.3 Dropouts and/or Discontinuations

Trial 1218.46:

In the randomized group of the trial, 5 subjects in the placebo arm (6.9%), 6 subjects in the L5 arm (4.2%), 3 subjects in the M500 arm (2.1%), 6 subjects in the M1000 arm (4.1%), 5 subjects in the L2.5+M500 arm (3.5%), and 3 subjects in the L2.5+M1000 arm (2.1%) reported AEs leading to discontinuation. Table 29 lists all the specific AEs resulting in discontinuation of subjects in the trial.

Overall, the largest number of dropouts occurred in the placebo arm, largely due to loss of glycemic control (3 subjects each with hyperglycemia and one subject with increased glycosylated hemoglobin), which would not be unexpected. Diarrhea and headache were the most frequently reported AE that led to treatment discontinuation and was only reported in the treatment arms with metformin therapy (e.g., M1000, L2.5+M500, L2.5+M1000).

Two subjects in the M500 arm reported treatment discontinuation due to reduced GFR. One subject (47828) had a low GFR at baseline (61 mL/min), which decreased to 49 mL/min even before the placebo run-in period and persisted throughout the trial (last value of calculated GFR was 49 mL/min), leading to subject discontinuation. The second subject (48154) had a baseline GFR of 76 mL/min that decreased to 58.8 mL/min after two weeks of M500 therapy.

Discontinuation due to cardiac disorders were reported for all active treatment groups, and all subjects who discontinued due to cardiac disorders were between 65 to 74 years of age with underlying cardiac disease.

Table 29: 1218.46 - Listing of AEs Leading to Discontinuation by Treatment Arm

Treatment arm	Subject ID	Age/ Gender	Preferred Term	Onset Day	Duration (days)	Serious	Outcome
Placebo	48950	69/F	Glycosylated hemoglobin increased	29	15	No	Recovered
	46452	62/M	Hyperglycemia	3	215*	No	Not recovered
	48591	56/F	Hyperglycemia	67	34	No	Recovered
	49041	64/M	Hyperglycemia	15	44	No	Recovered
	48338	52/M	Renal colic	136	2	No	Recovered
Lina 5	46913	58/M	Angina unstable	85	8	Yes	Recovered
			Left ventricular failure	86	7	Yes	Sequelae
			Myocardial infarction	20	31	Yes	Sequelae
	49565	61/M	Myocardial ischemia	1	87	Yes	Recovered
	48459	43/M	Abdominal pain	16	7	No	Recovered
	49052	77/M	GGT increased	87	183*	No	Not recovered
	48946	52/M	Hyperglycemia	48	228*	No	Not recovered
	48990	64/F	Headache	3	34	No	Recovered
	49621	47/M	Hyperchlorhydria	43	21	No	Recovered
	47828	57/F	GFR decreased	7	412	No	Sequelae
Met 500	48154	67/F	GFR decreased	1	15	No	Recovered
	49471	66/M	Myocardial infarction	130	1	Yes	Fatal
	48983	68/F	Diarrhea	14	6	No	Recovered
	49742	52/M	Hemorrhoids	17	2	Yes	Recovered
	49840	73/M	Femoral neck fracture	41	49	Yes	Recovered
Met 1000	46459	72/F	Diabetes mellitus	142	51*	No	Not recovered
	48458	49/F	Headache	34	4	No	Recovered
	47550	77/M	Nausea	79	4	No	Recovered
			Diarrhea	78	3	No	Recovered
	47941	65/F	Diarrhea	1	18	No	Recovered
	49846	65/F	Hepatic enzyme increased	180	53	No	Recovered
	48131	61/M	Muscle spasms	3	13	No	Recovered
	49484	43/M	Headache	2	4	No	Recovered
	46526	69/M	Angina pectoris	36	11	Yes	Recovered
	46207	63/M	Diarrhea	84	24	No	Recovered
Lina 2.5 + Met 500	47813	57/F	Headache	15	104	No	Recovered
	48063	79/F	Bradycardia	15	37	No	Recovered
			Peripheral edema	36	16	No	Recovered
			Dyspnea exertional	33	19	No	Recovered
			Nausea	17	30	No	Recovered
			Diarrhea	32	8	No	Recovered
	49485	40/F	Hyperglycemia	2	21	No	Recovered
	49509	44/F	Hyperglycemia	32	320*	No	Not recovered
	48470	55/M	Nausea	17	6	No	Recovered

Source: 1218.46 CTR, Listing 7.2.3

*censored; GFR=glomerular filtration rate; GGT=gamma-glutamyltransferase

Trial 1218.52:

Four subjects in the M1000 arm (2.4%), 5 subjects in the L2.5+M500 arm (2.2%), and 3 subjects in the L2.5 +M1000 arm (1.8%) reported AEs leading to discontinuation. Overall, the most frequent reason for study discontinuation was for decreased GFR of <60 mL/min, reported in two subjects in each arms treated with the coadministration of linagliptin and metformin. These subjects had a mild renal impairment at baseline, none of these subjects experienced severe renal impairment, and their GRF recovered to >60 mL/min upon discontinuation of study drug.

Table 30: 1218.52 - Listing of AEs Leading to Discontinuation by Treatment Arm

Treatment arm	Subject ID	Age/Gender	Preferred Term	Onset Day	Duration (days)	Serious	Outcome
M1000	49819	72/M	Cerebrovascular accident	55	31	Yes	Sequelae
	49044	44/M	Hyperglycemia	42	209*	No	Not recovered
	49667	60/M	Amylase increased	43	62*	No	Not recovered
	49616	45/F	Transaminases increased	1	57	No	Recovered
L2.5+M500	47571	65/F	Anemia	106	29	Yes	Recovered
	48012	74/M	GFR decreased	47	120	No	Recovered
	48087	70/F	GFR decreased	47	17	No	Recovered
	49789	41/M	Diabetes mellitus	34	126*	No	Not recovered
	48136	40/M	Glycosylated hemoglobin increased	43	unknown	No	Not recovered
L2.5+M1000	46044	73/M	GFR decreased	127	14	No	Recovered
	47021	62/F	GFR decreased	42	16	No	Recovered
	48949	66/M	Road traffic accident	71	1	Yes	Fatal

*censored; HO=hospitalization; LT=life-threatening; GFR=glomerular filtration rate

Source: 1218.52 CTR, Table 15.4.2.1:1, 15.4.2.1:2, 15.4.2.1:3

7.3.4 Significant Adverse Events

Adverse Events of Special Interest:

Due to our experience with other DPP-4 inhibitors, we had requested the applicant to analyze events of special interest to the class, including hypersensitivity reactions (i.e., angioedema, angioedema-like events, and anaphylaxis), renal events (e.g., renal failure, eGFR <60mL/min), hepatic events, severe cutaneous adverse reactions, and pancreatitis. The analysis of these AEs was done using the narrow standardized MedDRA queries (SMQ) as following:

- Hepatic events - narrow SMQs of “liver-related investigations, signs and symptoms”, “cholestasis and jaundice of hepatic origin”, “hepatitis, non-infectious”, and “hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions”
- Renal events - narrow SMQs of “acute renal failure”
- Hypersensitivity reactions - narrow SMQs of “anaphylactic reaction”, “angioedema”, and “asthma/bronchospasm”

- Severe cutaneous skin lesions - AEs of epidermal necrosis, dermatitis exfoliative, or drug eruptions included; also based on the narrow SMQ “severe cutaneous adverse reactions”
- Pancreatitis - AEs of pancreatitis; also based on the narrow SMQ “acute pancreatitis”

An overview of the reported AEs of interest based on narrow SMQ search is summarized in Table 31 for trial 1218.46 and Table 32 for trial 1218.52.

For trial 1218.46, there was only one hypersensitivity reaction of periorbital edema reported in L5 arm. This was of mild intensity, not serious, and the subject recovered from the event.

Similar incidence of hepatic events occurred in L5, M500, M1000, and L2.5/M500 treatment arms at 3.5%, 3.5%, 4.1%, and 3.5% respectively. Most frequently reported hepatic events were increased ALT.

Table 31: 1218.46 - Summary of pre-specified significant AEs by treatment arm

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)
Patients with hypersensitivity reactions ¹	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Periorbital oedema	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with hepatic events ²	0 (0.0)	5 (3.5)	5 (3.5)	6 (4.1)	5 (3.5)	2 (1.4)
Hepatic steatosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
ALT increased	0 (0.0)	3 (2.1)	2 (1.4)	5 (3.4)	2 (1.4)	2 (1.4)
AST increased	0 (0.0)	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	2 (1.4)
Blood bilirubin increased	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
GGT increased	0 (0.0)	1 (0.7)	2 (1.4)	0 (0.0)	1 (0.7)	1 (0.7)
Hepatic enzyme increased	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)
Perihepatic discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

¹ Based on narrow SMQs 'anaphylactic reaction', 'angioedema', and 'asthma-bronchospasm'.

² Based on narrow SMQs 'liver-related investigations, signs and symptoms', 'choleostasis and jaundice of hepatic origin', 'hepatitis, non-infectious', and 'hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions'.

Source: 1218.46 CTR, Table 12.3.3:1

For trial 1218.52, hepatic AEs were reported in 7 subjects in the M1000 arm (4.1%), 5 in the L2.5+M500 arm (2.2%), and one in the L2.5+M1000 arm (0.6%). The most commonly reported hepatic events were related to liver-related investigations such as increases in ALT, AST, hepatic

enzymes/aminotransferases, and GGT. Hepatic steatosis occurred in four of five subjects in the L2.5/M500 arm.

One subject with a history of eczema reported a mild urticaria in trial 1218.52, which resolved after four days of topical hydrocortisone treatment.

Table 32: 1218.52 - Summary of pre-specified significant AEs by treatment arm

	Met 1000 N (%)	Lina 2.5 + Met 500 N (%)	Lina 2.5 + Met 1000 N (%)
Number of patients	170	225	171
Patients with hypersensitivity reactions	0	0	1 (0.6)
Urticaria	0	0	1 (0.6)
Patients with hepatic events	7 (4.1)	5 (2.2)	1 (0.6)
Hepatic steatosis	1 (0.6)	4 (1.8)	0
ALT increased	2 (1.2)	2 (0.9)	1 (0.6)
AST increased	1 (0.6)	2 (0.9)	1 (0.6)
Hepatic enzyme increased	2 (1.2)	0	0
Transaminases increased	1 (0.6)	0	0
GGT increased	0	0	1 (0.6)
Hepatomegaly	1 (0.6)	1 (0.4)	0
Liver disorder	1 (0.6)	0	0
Portal hypertension	1 (0.6)	0	0

Source: 1218.52 CTR, Table 15.3.2.1:9, 15.3.2.1:11

In both 1218.46 and 1218.52 trials, there were no renal events, severe cutaneous skin lesions, or pancreatitis in any subject based on the SMQ search.

Hypoglycemia:

Hypoglycemic episodes were captured as adverse events in the trial, and summarized in Table 33 for trial 1218.46 and Table 34 for trial 1218.52.

For trial 1218.46, the incidence of hypoglycemia was low overall, and was most frequently reported in the M1000 and L2.5+M500 arms (5 subjects in each arm). The majority of subjects reported a single episode of hypoglycemia during the treatment period. No hypoglycemia was reported in the L2.5+M1000 arm. One severe hypoglycemic episode requiring assistance was reported in the M1000 arm. One metformin-treated subject had an episode of hypoglycemia while receiving rescue therapy.

In the open-label arm, one subject reported asymptomatic hypoglycemia with an onset of first episode of more than 28 days, and had four or more hypoglycemic episodes.

Table 33: 1218.46 - Summary of Hypoglycemia by Treatment Arm

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000
Number of patients, N (%)	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)
Number of patients with investigator-defined hypoglycaemia ¹ , N (% of patients treated)	1 (1.4)	0 (0.0)	2 (1.4)	5 (3.4)	5 (3.5)	0 (0.0)
Any asymptomatic hypoglycaemia ² N (% of patients with hypoglycaemia)	0 (0.0)	0 (0.0)	1 (50.0)	2 (40.0)	0 (0.0)	0 (0.0)
Any severe hypoglycaemic episode ³ , N (% of patients with hypoglycaemia)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Number of hypoglycaemic episodes per patient, N (% of patients with hypoglycaemia)						
1	0 (0.0)	0 (0.0)	1 (50.0)	4 (80.0)	4 (80.0)	0 (0.0)
2 to 3	1 (100.0)	0 (0.0)	1 (50.0)	1 (20.0)	1 (20.0)	0 (0.0)
Time to onset of first episode, N (% of patients with hypoglycaemia)						
≤7 days	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (20.0)	0 (0.0)
>7 days to ≤28 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)
>28 days	1 (100.0)	0 (0.0)	1 (50.0)	5 (100.0)	2 (40.0)	0 (0.0)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

¹ Patients may have had events in more than one category or had events not covered by the 4 categories. Thus the sum of patients with events in the 4 categories may differ from the number of patients with any hypoglycaemic event.

² Not accompanied by typical symptoms of hypoglycaemia but with measured plasma glucose concentration ≤70mg/dL

³ Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

Source: 1218.46 CTR, Table 12.2.2.4:1

For trial 1218.52, the incidence of hypoglycemia was higher in the coadministration arms: 3.1% in the L2.5+M500 arm and 2.3% in the L2.5+M1000 arm compared to 0.6% in the M1000 arm. The majority of subjects reported a single episode of hypoglycemia during treatment. The minimum plasma glucose level was ≥54 mg/dL in all cases except for one subject each in M1000 and L2.5+M500 who had a glucose level <54 mg/dL. No subject reported a severe hypoglycemia requiring assistance. No subjects were receiving rescue therapy during the hypoglycemic event.

Reviewer's comment: Trial 1218.52 demonstrated a higher incidence of hypoglycemia in the L+M coadministration arms compared to the metformin-alone treatment arm. In trial 1218.46, hypoglycemia occurred similar to or more often in the metformin alone treatment arm compared to the L+M treatment arm, and this trend of more hypoglycemic events in metformin arm was also observed in various pooled safety data. But safety data from 1218.46 and pooled data are limited to ≤24 weeks, and trial 1218.52 provides long-term

safety data. However, no conclusion can be drawn at this time since the safety data at week 54 are yet incomplete for 1218.52, and the incidence of hypoglycemia will have to be fully assessed when complete safety data becomes available for trial 1218.52.

Table 34: 1218.52 - Summary of Hypoglycemia by Treatment Arm

	Met 1000 N (%)	lina 2.5 + met 500 N (%)	lina 2.5 + met 1000 N (%)
Number of patients	170 (100.0)	225 (100.0)	171 (100.0)
Investigator-defined hypoglycaemia	1 (0.6)	7 (3.1)	4 (2.3)
Symptoms of hypoglycaemia, worst episode			
No	1 (100.0)	4 (57.1)	1 (25.0)
Yes	0 (0.0)	3 (42.9)	3 (75.0)
No assistance required, worst episode	1 (100.0)	7 (100.0)	4 (100.0)
Number of episodes per patient			
1	1 (100.0)	6 (85.7)	3 (75.0)
2 to 3	0 (0.0)	1 (14.3)	1 (25.0)
Time to onset of first episode [days]			
≤7	0 (0.0)	2 (28.6)	1 (25.0)
>7 to ≤28	0 (0.0)	2 (28.6)	0 (0.0)
>28	1 (100.0)	3 (42.9)	3 (75.0)
Minimum glucose level, worst episode [mg/dL]			
<54	1 (14.3)	1 (25.0)	
≥54 to ≤70	0 (0.0)	4 (57.1)	2 (50.0)
>70	1 (100.0)	1 (14.3)	1 (25.0)
Not measured	0 (0.0)	1 (14.3)	0 (0.0)
Characteristics of hypoglycaemic events ^{1,2}			
Any asymptomatic event	1 (100.0)	4 (57.1)	2 (50.0)
Any symptomatic event by PG level			
<54 mg/dL	0 (0.0)	0 (0.0)	1 (25.0)
≥54 and ≤70 mg/dL	0 (0.0)	1 (14.3)	1 (25.0)
>70 mg/dL	0 (0.0)	1 (14.3)	1 (25.0)
Not measured	0 (0.0)	2 (28.6)	0 (0.0)
Event requiring assistance (severe) ³	0 (0.0)	0 (0.0)	0 (0.0)

PG: plasma glucose

¹ Patients could be counted in more than 1 category

² Percent based on numbers of patients with a hypoglycaemic event

³ Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Source: 1218.52 CTR, Table 12.2.2.5:1

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

SAF-1:

Of 3084 subjects with T2DM who were treated with L+M therapy during Phase 2/3 trials, 71.9% experienced one or more AEs. The most frequently occurring AEs for L+M therapy were hypoglycemia (12.1%), hyperglycemia (11.1%), nasopharyngitis (9.2%), diarrhea (4.9%), and headache (4.9%). Cardiac disorders were reported infrequently during Phase 2/3 trials (4.7%).

Trial 1218.46:

The proportion of subjects with AEs were comparable between treatment arms: 54.2% in the placebo arm, 56.3% in the L5 arm, 52.1% in the M500 arm, 50.3% in the M1000 arm, 49% in the L2.5+M500 arm, and 56.6% in the L2.5+M1000 arm. The frequency of AEs occurring at an incidence of >2% in any treatment arm at the Preferred Term (PT) level is summarized by System Organ Class (SOC) in Table 35.

L+M vs respective monotherapies: A higher incidence of diarrhea was observed in the L+M arms compared to respective monotherapy arms. A higher incidence of nasopharyngitis in the L+M was observed compared to respective metformin monotherapy arms, but not for linagliptin monotherapy.

AEs by doses of metformin: The proportion of subjects who had AEs was similar for M500 and M1000 monotherapy arms. The L2.5+M500 had a slightly lower AEs compared to the L2.5+M1000 arm at 47.6 vs 53.8% respectively. GI disorders increased with increasing dose of metformin in both metformin monotherapy arms and L+M arms.

Nasopharyngitis: The PTs ‘nasopharyngitis’, ‘pharyngitis’, and ‘pharyngitis bacterial’ were combined since they all indicate nasopharyngitis events, and a higher incidence of nasopharyngitis was observed in the L2.5+M500 arm (10.5%), L2.5+M1000 arm (7%), and L5 arm (6.3%), compared to 4.8% in the M1000 arm and 2.8% in the placebo and M500 arms.

Investigations SOC: Increased ALT was most frequently observed in the M1000 arm (3.4%) compared to all the other treatment arms. Decreased GFR was most frequently observed in the placebo arm (5.6%) followed by the L2.5+M1000 arm (4.2%).

Table 35: 1218.46 - Summary of adverse events with $\geq 2\%$ incidence in any treatment arm at PT, sorted by the overall frequency and SOC

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)
Number of patients with any AE	39 (54.2)	80 (56.3)	75 (52.1)	74 (50.3)	70 (49.0)	81 (56.6)
Blood and lymphatic system disorders	2 (2.8)	1 (0.7)	3 (2.1)	1 (0.7)	2 (1.4)	3 (2.1)
Eosinophilia	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	4 (2.8)	4 (2.8)	1 (0.7)	2 (1.4)	1 (0.7)
Vertigo	0 (0.0)	2 (1.4)	3 (2.1)	1 (0.7)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	10 (13.9)	17 (12.0)	14 (9.7)	23 (15.6)	20 (14.0)	28 (19.6)
Constipation	1 (1.4)	2 (1.4)	3 (2.1)	0 (0.0)	2 (1.4)	1 (0.7)
Diarrhoea	2 (2.8)	5 (3.5)	3 (2.1)	8 (5.4)	7 (4.9)	11 (7.7)
Gastritis	2 (2.8)	1 (0.7)	1 (0.7)	0 (0.0)	4 (2.8)	3 (2.1)
Hyperchlorhydria	0 (0.0)	0 (0.0)	3 (2.1)	1 (0.7)	1 (0.7)	1 (0.7)
Nausea	0 (0.0)	1 (0.7)	0 (0.0)	5 (3.4)	4 (2.8)	3 (2.1)
Vomiting	1 (1.4)	2 (1.4)	0 (0.0)	1 (0.7)	3 (2.1)	0 (0.0)
General disorders and administration site conditions	5 (6.9)	9 (6.3)	14 (9.7)	12 (8.2)	3 (2.1)	10 (7.0)
Fatigue	1 (1.4)	4 (2.8)	1 (0.7)	5 (3.4)	1 (0.7)	1 (0.7)
Pyrexia	2 (2.8)	3 (2.1)	5 (3.5)	2 (1.4)	0 (0.0)	6 (4.2)
Infections and infestations	16 (22.2)	26 (18.3)	29 (20.1)	24 (16.3)	31 (21.7)	33 (23.1)
Gastroenteritis	1 (1.4)	3 (2.1)	2 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)
Influenza	3 (4.2)	6 (4.2)	7 (4.9)	5 (3.4)	6 (4.2)	1 (0.7)
Nasopharyngitis	1 (1.4)	8 (5.6)	4 (2.8)	4 (2.7)	12 (8.4)	6 (4.2)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)	0 (0.0)	3 (2.1)
Pharyngitis bacterial	1 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.1)	1 (0.7)
Respiratory tract infection	3 (4.2)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)
Upper respiratory tract infection	2 (2.8)	1 (0.7)	6 (4.2)	0 (0.0)	3 (2.1)	6 (4.2)
Urinary tract infection	2 (2.8)	2 (1.4)	4 (2.8)	3 (2.0)	2 (1.4)	7 (4.9)
Investigations	4 (5.6)	10 (7.0)	13 (9.0)	11 (7.5)	8 (5.6)	12 (8.4)
ALT increased	0 (0.0)	3 (2.1)	2 (1.4)	5 (3.4)	2 (1.4)	2 (1.4)
Blood amylase increased	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	3 (2.1)
Glomerular filtration rate decreased	4 (5.6)	5 (3.5)	4 (2.8)	3 (2.0)	2 (1.4)	6 (4.2)

Metabolism and nutrition disorders	12 (16.7)	10 (7.0)	16 (11.1)	11 (7.5)	16 (11.2)	7 (4.9)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	3 (2.1)
Hyperglycaemia	10 (13.9)	5 (3.5)	12 (8.3)	3 (2.0)	5 (3.5)	2 (1.4)
Hypoglycaemia	1 (1.4)	0 (0.0)	2 (1.4)	4 (2.7)	4 (2.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	5 (6.9)	13 (9.2)	8 (5.6)	13 (8.8)	13 (9.1)	14 (9.8)
Arthralgia	0 (0.0)	2 (1.4)	2 (1.4)	2 (1.4)	2 (1.4)	4 (2.8)
Back pain	2 (2.8)	5 (3.5)	0 (0.0)	5 (3.4)	2 (1.4)	8 (5.6)
Muscle spasms	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)	0 (0.0)
Pain in extremity	0 (0.0)	2 (1.4)	3 (2.1)	2 (1.4)	1 (0.7)	2 (1.4)
Nervous system disorders	3 (4.2)	11 (7.7)	20 (13.9)	5 (3.4)	15 (10.5)	13 (9.1)
Diabetic neuropathy	1 (1.4)	1 (0.7)	1 (0.7)	0 (0.0)	2 (1.4)	3 (2.1)
Headache	1 (1.4)	6 (4.2)	7 (4.9)	3 (2.0)	4 (2.8)	4 (2.8)
Paraesthesia	1 (1.4)	1 (0.7)	3 (2.1)	1 (0.7)	4 (2.8)	2 (1.4)
Psychiatric disorders	3 (4.2)	2 (1.4)	5 (3.5)	1 (0.7)	2 (1.4)	0 (0.0)
Anxiety	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	4 (2.8)	1 (0.7)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	2 (1.4)	4 (2.8)	3 (2.0)	4 (2.8)	5 (3.5)
Cough	1 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)	2 (1.4)	3 (2.1)
Vascular disorders	4 (5.6)	4 (2.8)	6 (4.2)	5 (3.4)	5 (3.5)	5 (3.5)
Hypertension	4 (5.6)	4 (2.8)	5 (3.5)	4 (2.7)	5 (3.5)	5 (3.5)

The number of patients with AEs in a SOC is based on all AEs within this SOC, not only on the most frequent AEs >2%.

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

Source: 1218.46 CTR, Table 12.2.2:1

Pooling of AE data across metformin doses: The AE data pooled across the metformin dose are summarized in Table 36. The SOC with the highest frequencies of AEs for L+M combination therapy were Infections and Infestations (22.4%) and Gastrointestinal disorders (16.8%). The AEs more frequently reported for L+M arm compared to placebo or monotherapy arms were nasopharyngitis (6.3%), diarrhea (6.3%), nausea (2.4%), and paresthesia (2.1%). The hypoglycemia reported in the L+M arm was low and similar to the placebo arm.

Table 36: 1218.46 - Summary of AEs ≥2% in any treatment arm when pooled by the metformin dose

System Organ Class/Preferred Term	Placebo N (%)	Lina N (%)	Met N (%)	Lina+Met N (%)
Number of patients	72 (100.0)	142 (100.0)	291 (100.0)	286 (100.0)
Number of patients with any AE, N (%)	38 (52.8)	78 (54.9)	144 (49.5)	145 (50.7)
Infections and infestations	16 (22.2)	26 (18.3)	53 (18.2)	64 (22.4)
Gastroenteritis	1 (1.4)	3 (2.1)	3 (1.0)	2 (0.7)
Influenza	3 (4.2)	6 (4.2)	12 (4.1)	7 (2.4)
Nasopharyngitis	1 (1.4)	8 (5.6)	8 (2.7)	18 (6.3)
Respiratory tract infection	3 (4.2)	1 (0.7)	0 (0.0)	2 (0.7)
Upper respiratory infection	2 (2.8)	1 (0.7)	6 (2.1)	9 (3.1)
Urinary tract infection	2 (2.8)	2 (1.4)	7 (2.4)	9 (3.1)
Metabolism and nutrition disorders	12 (16.7)	8 (5.6)	27 (9.3)	22 (7.7)
Hyperglycemia	10 (13.9)	5 (3.5)	15 (5.2)	7 (2.4)
Hypoglycemia	1 (1.4)	0 (0.0)	6 (2.1)	4 (1.4)
Psychiatric disorders	3 (4.2)	2 (1.4)	6 (2.1)	2 (0.7)
Anxiety	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	3 (4.2)	11 (7.7)	25 (8.6)	27 (9.4)
Headache	1 (1.4)	6 (4.2)	10 (3.4)	8 (2.8)
Paraesthesia	1 (1.4)	1 (0.7)	4 (1.4)	6 (2.1)
Vascular disorders	4 (5.6)	4 (2.8)	11 (3.8)	8 (2.8)
Hypertension	4 (5.6)	4 (2.8)	9 (3.1)	8 (2.8)
Gastrointestinal disorders	10 (13.9)	17 (12.0)	37 (12.7)	48 (16.8)
Diarrhea	2 (2.8)	5 (3.5)	11 (3.8)	18 (6.3)
Gastritis	2 (2.8)	1 (0.7)	1 (0.3)	7 (2.4)
Nausea	0 (0.0)	1 (0.7)	5 (1.7)	7 (2.4)
Musculoskeletal and connective tissue disorders	5 (6.9)	13 (9.2)	21 (7.2)	27 (9.4)
Back pain	2 (2.8)	5 (3.5)	5 (1.7)	10 (3.5)
General disorders and administration site conditions	5 (6.9)	9 (6.3)	26 (8.9)	13 (4.5)
Fatigue	1 (1.4)	4 (2.8)	6 (2.1)	2 (0.7)
Pyrexia	2 (2.8)	3 (2.1)	7 (2.4)	6 (2.1)
Investigations	2 (2.8)	8 (5.6)	17 (5.8)	9 (3.1)
Alanine aminotransferase increased	0 (0.0)	3 (2.1)	6 (2.1)	2 (0.7)
Glomerular filtration rate decreased	2 (2.8)	3 (2.1)	3 (1.0)	2 (0.7)

Source: Module 2.5 Clinical Overview, Table 5.3.2:1

In the open-label arm, 53% of subjects reported an AE, and the AE profile was similar to that of subjects in the L2.5+M1000 treatment arm in the randomized phase, with the exception of higher incidence of hyperglycemia (10.6%). Diarrhea (6.1%) and urinary tract infections (6.1%) were also frequently reported. No pancreatitis cases were reported.

Trial 1218.52:

In the M1000 arm, 42.3% reported an AE, compared to 37.2% in the L2.5+M500 and 38.6% in the L2.5+M1000 arm. Table 37 summarizes AEs with $\geq 2\%$ incidence in any treatment arm at the PT level. Diarrhea (4.1%) and back pain (2.3%) were most frequently reported in the L2.5+M1000 arm compared to the other treatment arms. The L+M treatment arms experienced more decreased GFR (2.2% in L2.5+L500 arm, 1.8% in L2.5+M1000 arm) compared to the M1000 arm (0.6%). Hypoglycemia was only reported in the L+M treatment arms. Hyperglycemia and diabetes mellitus were reported the least in the L2.5+M1000 arm.

Table 37: 1218.52 - Summary of adverse events with $\geq 2\%$ incidence in any treatment arm at Preferred Term during the treatment period - Treated Set

	Met 1000 N (%)	lina 2.5 + met 500 N (%)	lina 2.5 + met 1000 N (%)
Number of patients	170 (100.0)	225 (100.0)	171 (100.0)
Any AE	73 (42.9)	84 (37.3)	66 (38.6)
Gastrointestinal disorders	13 (7.6)	15 (6.7)	18 (10.5)
Diarrhoea	1 (0.6)	4 (1.8)	7 (4.1)
Infections and infestations	19 (11.2)	26 (11.6)	10 (5.8)
Bronchitis	2 (1.2)	5 (2.2)	0 (0.0)
Nasopharyngitis	4 (2.4)	4 (1.8)	3 (1.8)
Investigations	16 (9.4)	12 (5.3)	8 (4.7)
Blood creatine phosphokinase increased	4 (2.4)	1 (0.4)	1 (0.6)
Glomerular filtration rate decreased	1 (0.6)	5 (2.2)	3 (1.8)
Metabolism and nutrition disorders	18 (10.6)	27 (12.0)	11 (6.4)
Diabetes mellitus	8 (4.7)	9 (4.0)	3 (1.8)
Hyperglycaemia	8 (4.7)	13 (5.8)	2 (1.2)
Hypoglycaemia	0 (0.0)	6 (2.7)	3 (1.8)
Musculoskeletal and connective tissue disorders	8 (4.7)	12 (5.3)	12 (7.0)
Back pain	1 (0.6)	2 (0.9)	4 (2.3)

The number of patients with AEs in a SOC is based on all AEs within this SOC, not only on patients with the most frequent AEs (i.e. AEs with an incidence of $>2\%$).

Source: 1218.52 CTR, Table 12.2.2.1:1

SEA2:

As summarized in Table 38, the following AEs were observed with a higher frequency in the pooled L5+Met arm compared to the pooled Met arm: diarrhea, nasopharyngitis, arthralgia, and back pain. Hyperglycemia and hypoglycemia were observed more frequently in the pooled Met arm.

Table 38: SEA-2: Summary of AEs with $\geq 2\%$ incidence in any pooled treatment arm

SOC/PT	Met N(%)	L5+Met N(%)
Number of patients	539 (100)	879 (100)
Number of patients with any AE	278 (51.6)	459 (52.5)
Gastrointestinal disorders	65 (12.1)	115 (13.1)
Diarrhea	18 (3.3)	35 (4.0)
Nausea	11 (2.0)	17 (1.9)
Infections and Infestations	108 (20)	187 (21.4)
Influenza	18 (3.3)	27 (3.1)
Nasopharyngitis*	27 (5)	64 (7.3)
Upper respiratory tract infection	17 (3.2)	25 (2.9)
Metabolism and nutrition disorders	73 (13.5)	75 (8.6)
Hyperglycemia	44 (8.2)	38 (4.3)
Hypertriglyceridemia	11 (2)	5 (0.6)
Hypoglycemia	11 (2)	7 (0.8)
Musculoskeletal and connective tissue disorders	40 (7.4)	90 (10.3)
Arthralgia	9 (1.7)	18 (2.1)
Back pain	10 (1.9)	22 (2.5)
Nervous system disorders	35 (6.5)	65 (7.4)
Headache	18 (3.3)	24 (2.7)
Vascular disorders	20 (3.7)	33 (3.8)
Hypertension	16 (3)	25 (2.9)

*‘Nasopharyngitis’ include MedDRA PTs of nasopharyngitis, pharyngitis, and pharyngitis bacterial

Source: ISS, Table 6.1

SAF-8:

About 36% of healthy subjects reported AEs during the six Phase 1 trials. There were no deaths, SAEs, or discontinuation due to AEs. The AEs that occurred $\geq 2\%$ were headache (15.3%), diarrhea (9%), nausea (4.8%), vomiting (3.1%), nasopharyngitis (2.8%), and abdominal pain-related (including both ‘abdominal pain’ and ‘abdominal pain upper’ PTs, 2.5%).

Reviewer's comment: The applicant proposed inclusion of the following adverse reactions in section 6.1 of labeling from their analyses of safety data with coadministration of linagliptin and metformin (regardless of investigator assessment of causality):

- 1) Adverse reactions $\geq 5\%$ in the linagliptin + metformin arm (pooled regardless of metformin dose) and greater than placebo arm from the 24-week factorial design trial 1218.46
- 2) Adverse reactions $\geq 5\%$ in the linagliptin + metformin arm and greater than placebo + metformin arm from SEA-2
- 3) Hypoglycemia from SEA-2

Since the analysis of AEs in SEA-2 (#2) did not provide a different pattern of AEs from the AE data in trial 1218.46 (#1), I recommend deletion of #2 from their proposed labeling. In addition, I recommend presenting hypoglycemia data from trial 1218.46 rather than SEA-2, since we are only including safety data from 1218.46 in other aspects of AE in linagliptin + metformin section.

7.4.2 Laboratory Findings

Standard safety laboratory parameters for chemistry and hematology were obtained at baseline, Week 12, and at the end of treatment period (Week 24) in trial 1218.46. The mean (SE) change from baseline for the laboratory parameters is summarized in Table 39.

Differences between treatments were observed in the mean change from baseline for alkaline phosphatase, with decreases in the active treatment ranging from 23 U/L in the L2.5+M1000 arm to 8 U/L in the L5 arm. No decrease or increase was observed in the placebo group. This decrease in alkaline phosphatase is commonly observed in diabetes trials, and may be related to improved glycemic control with active treatment.

Small mean differences in other parameters were also not clinically significant.

Table 39: 1218.46 - Mean change (SE) from baseline to last value on treatment in laboratory parameters by treatment group

Laboratory Test	Placebo	M500	M1000	L5	L2.5+ M500	L2.5+ M1000
Chemistry						
Alkaline phosphatase (U/L)	0 (45)	-11 (37)	-18 (34)	-8 (29)	-17 (39)	-23 (37)
ALT (U/L)	-6 (23)	-3 (23)	1 (28)	-4 (15)	2 (33)	-3 (28)
AST (U/L)	-4 (17)	-3 (20)	2 (27)	-1 (13)	3 (32)	-2 (25)
GGT (U/L)	2 (37)	-11 (71)	-11 (36)	2 (31)	-4 (50)	-7 (37)
BUN (mmol/dL)	0.1 (0.4)	0 (0.3)	0 (0.4)	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)
Bicarbonate (mmol/L)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)
Calcium (mmol/L)	-0.03 (0.11)	-0.04 (0.1)	-0.02 (0.13)	-0.04 (0.1)	-0.04 (0.12)	0 (0.13)
Chloride (mmol/L)	0 (3)	1 (4)	0 (3)	0 (3)	1 (3)	1 (3)
Creatinine (mg/dL)	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)
Phosphate (mmol/L)	0.01 (0.11)	0.01 (0.11)	0 (0.11)	-0.02 (0.1)	0 (0.11)	0.01 (0.11)

Potassium (mmol/L)	0 (0.4)	0 (0.4)	0 (0.4)	0 (0.3)	0 (0.4)	0 (0.4)
Sodium (mmol/L)	0 (4)	0 (4)	0 (4)	1 (4)	0 (4)	1 (4)
Total bilirubin (mg/dL)	0 (0.1)	-0.1 (0.2)	0 (0.2)	0 (0.1)	0 (0.2)	-0.1 (0.2)
Total protein (g/dL)	0 (0.4)	-0.1 (0.4)	-0.1 (0.4)	0 (0.3)	-0.1 (0.4)	-0.1 (0.4)
Albumin (g/dL)	0 (0.4)	0 (0.4)	0 (0.4)	-0.1 (0.4)	-0.1 (0.4)	0 (0.4)
Uric acid (mg/dL)	0 (1)	0.3 (1.1)	0.4 (1.2)	0.2 (1)	0.3 (1.2)	0.7 (1.3)
Glucose (mg/dL)	-10 (57)	-25 (60)	-35 (46)	-17 (47)	-40 (54)	-51 (49)
Total cholesterol (mg/dL)	0 (28)	-5 (20)	-5 (30)	3 (26)	-4 (31)	-6 (28)
HDL (mg/dL)	0 (8)	3 (10)	2 (8)	2 (9)	1 (9)	1 (10)
LDL (mg/dL)	-3 (35)	-9 (28)	-7 (37)	5 (33)	-6 (39)	-8 (37)
Triglyceride (mg/dL)	6 (79)	-3 (66)	-17 (93)	-8 (77)	-5 (92)	-10 (74)
LDH (U/L)	-1 (15)	-4 (19)	-6 (14)	0 (14)	-2 (16)	-6 (16)
Creatinine kinase (U/L)	-9 (89)	5 (148)	-11 (79)	15 (116)	0 (132)	-39 (303)
Amylase (U/L)	1 (10)	5 (20)	3 (14)	1 (14)	5 (23)	9 (19)
CK-MB enzymatic (ug/L)	-1 (2)	0 (2)	0 (4)	-2 (4)	-1 (2)	-1 (2)
Hematology						
Hematocrit (%)	0.8 (3.7)	-0.2 (3.4)	-0.2 (3.7)	0.3 (2.9)	-0.8 (3.4)	-0.7 (3.1)
Hemoglobin (gm/dL)	0.2 (1.2)	-0.2 (0.8)	-0.2 (0.9)	0 (0.7)	-0.3 (0.9)	-0.3 (1.0)
RBC count	0.1 (0.3)	0 (0.3)	-0.1 (0.3)	0.1 (0.3)	-0.1 (0.4)	-0.1 (0.4)
WBC count	0.1 (1.8)	0.2 (1.3)	0.3 (1.3)	0.5 (1.3)	0.2 (1.5)	0.5 (1.5)
Platelets	-2 (36)	4 (29)	12 (37)	0 (28)	-1 (38)	8 (38)
Neutrophils (%)	0 (7)	1 (8)	2 (8)	4 (8)	2 (9)	3 (9)
Basophils (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eosinophils (%)	2 (15)	0 (3)	0 (2)	0 (1)	0 (2)	0 (1)
Lymphocytes (%)	0 (4)	0 (4)	0 (3)	0 (3)	0 (4)	0 (4)
Monocytes (%)	0 (1)	0 (1)	0 (1)	0 (2)	0 (1)	0 (2)

Source: 1218.46 CTR, Table 15.3.3.1:1

Similarly, in the open-label arm, no clinically relevant findings compared to baseline were seen for any of the safety laboratory parameters.

The applicant also analyzed possible clinically significant abnormalities from baseline and the number (%) of subjects who met the criteria, which showed no clinically significant trends in the co-administration L+M arms when compared to placebo or metformin or linagliptin arms.

The percentage of subjects meeting the possible clinically significant abnormalities was similar between the treatment groups, except in the following categories which had a between-group difference $\geq 2\%$:

- Increased amylase ($>1.5 \times \text{ULN}$) occurred in 3.6% in the L2.5+M1000 arm, compared to 1.5% in L2.5+M500 and 1.4% in M500 arm.
- Increased triglycerides of 6.5%, 6%, 5.9%, and 5.7% in the placebo, L2.5+M500, M1000, and L3.5+M1000 arms respectively, compared to 2.9% in M500 and 3.1% in L5 arms.

To support the analyses of liver-related AEs, potential Hy's law cases were evaluated, as defined by the presence of ALT or AST (or both) $>3 \times \text{ULN}$, total bilirubin $\geq 2 \times \text{ULN}$, and ALP $\leq 2 \times \text{ULN}$. No subjects met the Hy's law criteria.

In order to support the analysis of renal function during the trial, eGFR was categorized according to the MDRD staging, and the frequency of subjects with shifts in categories of renal impairment stage was investigated. The renal function was also categorized based on the eCcr values calculated using the Cockcroft-Gault formula. The stages of renal function were specified as:

Stage	eGFR [mL/min]	eCcr [mL/min]	Description
1	≥90	≥80	Normal renal function
2	60 to <90	50 to <80	Mild renal impairment
3	30 to <60	30 to <50	Moderate renal impairment
4 to 5	<30	<30	Severe renal impairment

In all treatment groups, there was a slight decrease in the percentage of subjects with normal/mild renal impairment from baseline to last visit: 98.2 to 96.5% in placebo, 99.2 to 96.9% in L5 arm, 97.7 to 97% in M500 arm, 99.2 to 98.4% in M1000 arm, 99.2 to 98.4% in L2.5/M500 arm, and 99.3 to 94.2% in L2.5/M1000 arm. Similarly, there was a slight increase in the percentage of subjects with moderate renal impairment from baseline to last visit: 1.8 to 3.5% in placebo, 0.8 to 3.1% in L5 arm, 2.3 to 3% in M500 arm, 0.8 to 1.6% in M1000 arm, 0.8 to 1.6% in L2.5/M500, and 0.7 to 5.1% in L2.5/M1000 arm. In the L2.5/M1000 arm, one subject shifted to stage 4/5 by the end of the trial.

In the open-label arm, 2 subjects shifted from moderate renal impairment to normal/mid renal impairment.

7.4.3 Vital Signs

The vital signs were measured at every visit except at Week 2. The mean changes in vital signs from baseline to the last value during the treatment period are summarized in Table 40. Overall, the changes in vital signs were minimal and not clinically significant. Additional analyses of outliers or shifts from normal to abnormal did not show any significant changes.

The mean changes in the vital signs were also minimal and not clinically significant in the open-label arm.

Table 40: 1218.46 - Mean change (SD) from baseline to last value on treatment in vital signs by treatment group

Vital signs	Placebo	L5	M500	M1000	L2.5+ M500	L2.5+ M1000
Systolic BP (mmHg)	0.14 (15.16)	-1.09 (12.54)	0.62 (11.79)	0.11 (13.32)	0.17 (13.11)	-0.34 (13.40)
Diastolic BP (mmHg)	0.24 (8.83)	-0.34 (7.64)	-0.29 (7.22)	-0.36 (8.96)	0.89 (8.63)	-1.10 (8.74)
Pulse rate (bpm)	-0.89 (8.03)	0.6 (9.88)	0.53 (8.87)	0.74 (9.96)	-0.04 (9.35)	-0.47 (9.04)

Source: 1218.46 CTR, Table 12.5.1:1, 12.5.1:2

7.4.4 Electrocardiograms (ECGs)

ECGs were recorded at the Screening visit, baseline, and at the end of trial. Any clinically significant new findings in the ECG measurements after the screening ECGs were reported as an AE, and no additional analyses were conducted by the applicant. The events under cardiac disorder did not show any significant ECG-related AEs.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Neither linagliptin nor metformin are proteins, and thus they are unlikely to cause immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The linagliptin dose to be marketed as part of the FDC is a single daily dose (5 mg), if approved. The FDC will have three different dose strengths available in the metformin component, and previous clinical experience with metformin has demonstrated that gastrointestinal AEs such as nausea, abdominal pain, and diarrhea are related to dose.

7.5.2 Time Dependency for Adverse Events

The applicant conducted time to onset for AEs by analyzing those subjects who participated in 1218.46 and entered 1218.52 and maintained the same treatment throughout both trials. Analyses of AEs by 26 week interval were conducted. It showed that the incidence of gastrointestinal AEs such as diarrhea and nausea were most frequently reported during the first 26 weeks of therapy, and declined over time. This is not surprising given that most subjects experience gastrointestinal AEs upon initiating metformin, and develop tolerance over time.

7.5.3 Drug-Demographic Interactions

No difference in the rate of AEs in different demographic subgroups was detected during my review.

7.5.4 Drug-Disease Interactions

The impact of hepatic impairment on the safety profile of linagliptin was reviewed in the linagliptin NDA (201280), where the overall number of subjects with an AE were higher in subjects with hepatic impairment (80% placebo vs. 66.7% linagliptin) compared to those without hepatic impairment. The overall number of subjects with impairment was very small in the linagliptin clinical program. No trends were noted.

Subjects with renal impairment will be at a higher risk for lactic acidosis when receiving metformin therapy, as noted in the metformin labeling. The applicant proposes to include similar contraindication for renal impairment in the linagliptin/metformin FDC labeling as metformin. I agree with this proposal.

7.5.5 Drug-Drug Interactions

Linagliptin and metformin have not been shown to affect the PK of each other, and thus is not expected to increase interactions with other drugs when co-administered. Please see the linagliptin and metformin labeling for a complete drug-drug interactions expected with each individual product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity studies were conducted with the linagliptin and metformin combination. Neither linagliptin nor metformin are genotoxic and neither is considered to pose a significant carcinogenic risk at the clinical exposure. In the clinical safety data thus far, trends showing increased neoplasms were not observed with either linagliptin or metformin as monotherapy or combination therapy.

7.6.2 Human Reproduction and Pregnancy Data

Linagliptin is pregnancy category B, reflecting that there are no adequate and well-controlled studies in pregnant women. Linagliptin was not teratogenic in animal studies at multiples of clinical exposure. Animal data have shown that linagliptin is excreted in milk, but it is unknown whether linagliptin is excreted in human milk.

Case reports associated with pregnancy were reviewed under linagliptin (NDA 201280), and one case of pregnancy who had an induced abortion was reported under this NDA. One additional pregnancy was reported in the 4-month safety update. A 35-year old woman (48559) who received L2.5+M1000 BID had a positive pregnancy test about 2 months after starting the

extension trial 1218.52. Study drugs were discontinued immediately. A diagnosis of severe holoprosencephaly was made during a routine ultrasound evaluation.

Metformin is also pregnancy category B. Metformin is not described as teratogenic at the clinical exposures in the current labeling, and previous animal studies with metformin did not suggest teratogenicity. In the nonclinical program for this NDA submission, a notable new toxicity suggesting potential metformin-related teratogenicity was indentified, as noted in section 4.3. The applicant conducted studies showing that metformin at 10- to 20-times human exposure caused skeletal malformations in Wistar Han rats. Combination treatment with linagliptin did not have any effect on the metformin-related malformations. Please see Dr. Carlson's review for full details.

Metformin is also shown to be excreted in milk in animal studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant originally requested a waiver from the PREA requirement to conduct pediatric studies with linagliptin/metformin FDC, because the fixed dose combination of linagliptin and metformin is unlikely to be used in a substantial number of pediatrics since the fixed dose combination does not allow flexibility in treatment with regard to dose and posology in the pediatric population up to the age of 18. The sponsor stated that the need for more individualized therapy in this population can be met by coadministration of the single components.

The Pediatric Review Committee (PeRC) had recently reviewed other DPP-4 inhibitor and metformin FDC (i.e., saxagliptin/metformin XR FDC NDA 200-678, sitagliptin/metformin XR NDA 202-270) and waived pediatric studies in subjects 0-9 years but imposed deferred studies in subjects 10-16 years.

Given this precedent, and with the possibility that linagliptin/metformin FDC can be used in the pediatric population, the same should be required for linagliptin/metformin FDC. A request was sent to the sponsor in the 74 day letter to propose a pediatric study plan.

On June 13, 2011, the applicant submitted a revised pediatric development plan. It included a waiver for subjects aged 0-9 years (inclusive) because T2DM is infrequently seen in children under the age of 12 and rarely seen in newborns, infants, and toddlers. The applicant also requested deferral of pediatric studies in subjects aged 10-16 years (inclusive) since they plan to conduct studies in the current linagliptin pediatric program, which will provide adequate data to assess the safety and effectiveness of the use of linagliptin and metformin. The pediatric program for linagliptin monotherapy will assess the co-administration of linagliptin and metformin in T2DM, in (b) (4) subjects who cannot achieve adequate glycemic control on background metformin therapy.

Although other DPP-4 inhibitor and metformin FDC have required swallowability assessment (i.e., saxagliptin/metformin XR FDC, sitagliptin/metformin XR), the tablet size of the linagliptin and metformin FDC tablets are comparable in size to the metformin tablets (16.2 x 8.5 x 5.8 mm for the 2.5/500 tablet, 21 x 9.62 x 7.6 mm for the 2.5/1000 mg tablet compared to 12.2 mm x 5.2 mm for Glucophage 500 mg tablet, and 19.2 x 10.7 x 6.5 mm for Glucophage 1000 mg tablet). Therefore, I do not believe that any additional studies to evaluate swallowability would be necessary.

The applicant proposed that the two trials that are required to satisfy Pediatric Research Equity Act (PREA) Post Marketing Requirements (PMR) under linagliptin (NDA 201-280) fulfill the PREA requirement for this linagliptin/metformin FDC:

- Study 1218.56: A 12-week randomized, double-blind, placebo-controlled, dose-finding study evaluating at least two doses of linagliptin (1 mg and 5 mg) as monotherapy in pediatric patients ages 10 to 16 years (inclusive) to evaluate the pharmacokinetics, pharmacodynamics, and efficacy of linagliptin.

(b) (4)



The pediatric plan was presented and discussed with the PeRC on October 12, 2011, and the PeRC agreed that the PREA requirements for the linagliptin/metformin FDC can be fulfilled with two PREA studies under linagliptin NDA 201-280.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose, potential for abuse, or withdrawal and rebound were noted for linagliptin monotherapy or linagliptin and metformin combination therapy.

7.7 Additional Submissions / Safety Issues

The applicant initially proposed the trade names (b) (4) for linagliptin/metformin FDC. The Division of Medication Error and Prevention Analysis

(DMEPA) found these proposed trade names unacceptable due to potential medication errors. Subsequently, on August 17, 2011, the applicant submitted (b) (4) Jentadueto as possible trade names, which is currently under review by DMEPA.

8 Postmarket Experience

No postmarketing data is available at the time of the NDA submission and 4MSU (dated April 29, 2011), since linagliptin is not marketed anywhere as monotherapy or in any combination. Linagliptin was approved in the US on May 2, 2011.

9 Appendices

9.1 Literature Review/References

Relevant references are cited within relevant sections of this clinical review.

9.2 Labeling Recommendations

Please refer to the following sections of this review for some of my labeling recommendations:

- 7.4.1 Common Adverse Events
- 7.5.4 Drug-Disease Interaction

Additional labeling recommendations are:

- Although the applicant is referencing Glucophage, include the safety information from Glumetza in the labeling since it has the most recent information related to metformin safety. Glumetza was recently updated in April 2011.

- Delete [REDACTED] (b) (4)

- Delete [REDACTED] (b) (4)

At the time of this review, labeling negotiations are still ongoing with the applicant.

9.3 Advisory Committee Meeting

Not applicable.

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

/s/

HYON J KWON
10/14/2011

ILAN IRONY
10/14/2011
I concur with Dr. Kwon's recommendation and review.

CLINICAL FILING CHECKLIST FOR NDA/BLA

NDA/BLA Number: 201281

**Applicant: Boehringer
Ingelheim**

Stamp Date: January 19, 2011

**Drug Name: Linagliptin +
Metformin FDC tablets**

NDA/BLA Type: 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(2); linagliptin (NDA 201-280) and metformin (Glucophage BMS)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	x			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			One BA and five BE phase 1 studies; one

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 - 1218.46; A Phase III randomized, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naive or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycemic control Indication: treatment T2DM Pivotal Study #2 Indication:				pivotal phase 3 study with factorial design for 24 weeks (1218.46); and one 54-week extension of Study 1218.46 (1218.52)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		3084 T2DM patients received linagliptin + metformin; of these, 1342 (43.5%) were recruited in Europe, 1038 (33.7) in Asia, 360 (11.7%) in South America, 291 (9.4%) in North America, and 53 (1.7%) in Africa. None of the phase 2 or 3 trials included US subjects.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	Addressed in linagliptin NDA 201280
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			A total of 3084 patients with T2DM received treatment with linagliptin + metformin; of these, 2585 were treated for at least 24 weeks and 1749 for at least 52 weeks
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			AEs coded using version 13.0 of MedDRA
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			Hypersensitivity reactions, severe cutaneous reactions, renal events, hepatic events, and pancreatitis
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			Yes from clinical standpoint, otherwise defer to other disciplines
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver for up to the age of (b)(4) citing inappropriateness of FDC due to the need for flexibility in treatment in children/adolescent population
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		see #17 above
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	No composite endpoint in the pivotal study
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes__

If the Application is not fileable from the clinical 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.

Hyon Kwon, PharmD, MPH	3/1/2011
Reviewing Medical Officer	Date
Ilan Irony, MD	3/1/2011
Clinical Team Leader	Date

MEMORANDUM

Filing Meeting: March 1, 2010
NDA 201281
Drug: Linagliptin + Metformin FDC tablets
Sponsor: Boehringer Ingelheim
Clinical Reviewer: Hyon J. Kwon, PharmD, MPH
Date received: January 19, 2011
PDUFA date: November 19, 2011

Assessment:

From the clinical standpoint, the NDA is fileable.

Background:

Boehringer Ingelheim has developed a film-coated, fixed-dose combination (FDC) product containing the active ingredient of linagliptin, a DPP-4 inhibitor, and metformin hydrochloride. The proposed doses of linagliptin/metformin FDC are 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg to be given twice daily.

The NDA for linagliptin was submitted for monotherapy at 5 mg daily dose for the treatment of T2DM, and is currently under review with the PDUFA goal date of May 2, 2011. Metformin was approved for treatment of T2DM in 1994.

The applicant proposes to use the FDC product as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

The applicant submitted six phase 1 trials, which included one bioavailability and five bioequivalence trials. The principle efficacy for the FDC is based on one pivotal phase 3 trial (1218.46), which is a factorial design comparing the efficacy of combination with the individual components of FDC in T2DM. The sponsor also included an interim analyses of a 54-week extension study of 1218.46 (1218.52).

Study 1218.46 was a randomized, double-blind, placebo-controlled, parallel group trial comparing the efficacy and safety of the free dose combination of linagliptin 2.5 mg plus metformin 500 mg and linagliptin 2.5 mg plus metformin 100 mg twice daily, with the individual components of metformin (500 mg or 1000 mg twice daily) and linagliptin (5 mg once daily) in drug naive or previously treated T2DM patients with insufficient glycemic control. The primary endpoint was the change of HbA1c from baseline to Week 24.

Study number/ locations; reference	Study characteristics	Treatments	Numbers randomized	Numbers evaluated for efficacy (FAS)
1218.46/ Europe, Canada, Mexico, India, Russia, Tunisia; [U10-2372, Module 5.3.5.1]	Pivotal double-blind placebo-controlled efficacy study; 24 weeks	<u>Double-blind</u>		
		L+M 2.5/500 mg bid	143	137
		L+M 2.5/1000 mg bid	143	140
		M 500 mg bid	144	141
		M 1000 mg bid	147	138
		L 5mg qd	142	135
		Placebo	<u>72</u>	<u>65</u>
		Total	791	756
1218.52°/ Countries from Study 1218.46; [U10-2442, Module 5.3.5.1]	Double-blind, randomized ext. study for 1218.46; 54 weeks	<u>Open label</u>		
		L+M 2.5/1000 mg bid	NA	66
		Metformin 1000	171	170
		L+M 2.5/500	225	225
		<u>L+M 2.5/1000</u>	<u>171</u>	<u>170</u>
		Total	567	565

L=linagliptin, M=metformin, SU=sulfonylurea

Site Inspections:

In Study 1218.46, the pivotal phase 3 trial for the FDC, India enrolled the largest number of subjects (31.5%). The linagliptin monotherapy NDA is supposed to inspect the site with Dr. Matthew Thomas, so the next top three Indian sites that randomized the most subjects are suggested for foreign inspections, as highlighted in Table 1. Although Mexico had one large site and did randomize a large number of subjects in Study 1218.46 (11.8%), DSI had previously recommended against site inspection in Mexico due to travel warnings. Final sites to be inspected will be determined based on further discussion with the DSI.

Table 1: List of Top Ten Sites That Randomized Subjects in Study 1218.46

Center Number	Number of randomized subjects	Country	Principal Investigator
91016	38	India	Thomas, Matthew
52002	35	Mexico	Sauque-Reyna, Leobardo
91015	33	India	Krishancharya, Vyankatesh Shivane
91004	28	India	Srikanta, Sathyanarayana
91013	24	India	Deshmukh, Vaishali
91014	23	India	Gupta, Sunil
70006	20	Russia	Antsiferov, Mikhail B.
49003	19	Germany	Bouzo, Hischam
91010	19	India	Mutha, Abhay
2161	17	Tunisia	Houissa Slimane, Hedia

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/s/

HYON J KWON
03/02/2011

ILAN IRONY
03/03/2011
I concur with Dr. Kwon the application is fileable.