

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201281Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 201281 / Sequence 0000

Drug Name: Linagliptin/Metformin Hydrochloride Tablets

Indication(s): To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Date(s): January 19, 2011

Review Priority: Standard (10-month)

Biometrics Division: Division of Biometrics 2 (HFD-715)

Statistical Reviewer: Wei Liu, Ph.D.

Concurring Reviewers: J. Todd Sahlroot, Ph.D. (Deputy Director)

Medical Division: Metabolism and Endocrinological Products (HFD-510, DMEP)

Clinical Team: Hyon Kwon, M.D.
Ilan Irony, M.D. (Team Leader)

Project Manager:

Keywords: NDA review, clinical studies, factorial design

Table of Contents

LIST OF TABLES (OPTIONAL)	3
LIST OF FIGURES (OPTIONAL)	3
1. EXECUTIVE SUMMARY	4
TABLE 1.1. GLYCEMIC PARAMETER HbA1C AT WEEK 24 FOR LINAGLIPTIN AND METFORMIN, ALONE AND IN COMBINATION IN PATIENTS WITH TYPE 2 DIABETES (LOCF).....	4
2. INTRODUCTION	6
2.1 OVERVIEW	6
2.2 DATA SOURCES.....	7
3. STATISTICAL EVALUATION	8
3.1. DATA AND ANALYSIS QUALITY	8
3.2. EVALUATION OF EFFICACY	9
3.3. EVALUATION OF SAFETY.....	19
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	21
5. SUMMARY AND CONCLUSIONS	25
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE.....	25
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	26
5.3 LABELLING COMMENTS	27
APPENDIX I. TIME COURSES OF HbA1C CHANGES FROM BASELINE BETWEEN ACTIVE TREATMENTS AND PLACEBO.	29
APPENDIX II. FOREST PLOTS OF HbA1C CHANGES FROM BASELINE BETWEEN ACTIVE TREATMENTS AND PLACEBO IN SUBGROUPS AT WEEK 24.	30
SIGNATURES/DISTRIBUTION LIST (OPTIONAL)	33
CHECK LIST	34

LIST OF TABLES (Optional)

Table 2.1.1: List of Studies Designed to Assess Safety and Efficacy	7
Table 3.2.1. Patient disposition and demographic information	11
Table 3.2.2. Glycemic Parameters (HbA1c) at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes	15
Table 3.2.3. Glycemic Parameters (Fasting Plasma Glucose) at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes	16
Table 3.3.1. List of Adverse Events by Treatments on All Randomized Patients with Type 2 Diabetes	19
Table 3.3.2. List of Laboratory Assays That Were Significantly Worse on Patients Treated by Lina 2.5 mg + Met 500 mg Twice Daily Versus At Least One Component	20
Table 3.3.3. List of Laboratory Assays That Were Significantly Worse on Patients Treated by Lina 2.5 mg + Met 1000 mg Twice Daily Versus At Least One Component	20

LIST OF FIGURES (Optional)

Figure 3.2.1. Overview of the study design	10
Figure 3.2.2. Baseline Levels of HbA1c in Different Treatment Groups	12
Figure 3.2.3. HbA1c Changes from Baseline Over 24 Weeks with Linagliptin + Metformin, Alone and in Combination in Study 46.	17
Figure 3.2.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels A: Linagliptin 5 mg and placebo, B: Metformin 500mg and placebo, C: Linagliptin 2.5 mg+Metformin 500mg and placebo, D: Metformin 1000mg and placebo, and E: Linagliptin 2.5 mg+Metformin 1000mg and placebo, respectively, in Study 46 to Week 24 (LOCF).	18
Figure 4.1.2. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 2.5 mg+Metformin 1000mg Twice Daily and Metformin 1000mg Twice Daily Treatments in Study 46 at Week 24.	22
Figure 4.1.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 2.5 mg+Metformin 500mg Twice Daily and Linagliptin 5 mg Once Daily Treatments in Study 46 at Week 24.	23
Figure 4.1.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 2.5 mg+Metformin 500mg Twice Daily and Metformin 500mg Twice Daily Treatments in Study 46 at Week 24.	24

1. EXECUTIVE SUMMARY

This statistical review covers one randomized trial of co-administered linagliptin and metformin (Study 46). Other (Lina + Met) combination trials submitted by the sponsor (Studies 17, 18 and 20) were reviewed in NDA 202180, the original submission for linagliptin, therefore were not reviewed as part of the current submission.

Confirmation of efficacy: The results of the pivotal study 1218.46 support the efficacy of linagliptin add-on to metformin hydrochloride at fixed dose as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus after 24 weeks of treatment based HbA1c reduction. Particularly, the combination treatment is statistically superior to the placebo and to each corresponding component treatment after 24 weeks treatment at a 0.05 level (two-sided).

Table 1.1. Glycemic Parameter HbA1c at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes (LOCF)

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)

(* the numbers were based on LOCF population)

The results from the sensitivity analyses (such as MMRM, completers, and per protocol) and key secondary endpoint, fasting plasma glucose level, support the superior of the combination to the placebo and to each corresponding component treatment on both HbA1c and FPG reductions after 24 weeks treatment at a 0.05 level (two-sided).

Subgroup analyses suggest that females derive greater benefit from adding either Lina or Met to the other drug than do males.

There were no significant differences in adverse event rates between each (Lina+Met) combination and its components. Laboratory assays suggest significant elevations in some immune system reactions in patients treated by the combined (Lina+Met) drugs versus those by the component drugs.

The results from non-LOCF analysis methods (this reviewer's MMRM, completers, and per protocol) showed that linagliptin 5 mg was not statistically superior to placebo at the 0.05 alpha

level (two-sided). Estimated treatment differences for HbA1c were -0.1 or -0.2. These smaller treatment differences compared to the LOCF results were due primarily to differences in the estimated changes from baseline in the placebo group which were much lower (i.e., greater improvement) in the sensitivity analyses. It is noted also in the LOCF population that the percentages of 7% HbA1c responders (see Table 1 above) for placebo (10.8%) and linagliptin (10.4%) were identical raising questions about the efficacy of linagliptin 5 mg QD in study 46.

This finding is, however, not critical to the determination of efficacy of the combinations (Lina+Met) since the determination does not require efficacy data from placebo and the data from linagliptin monotherapy is used only to support the efficacy of metformin in the combination. Nevertheless the efficacy of linagliptin monotherapy needs to be considered in the context of the submission.

Labelling Recommendations:

The statistical review addresses statements in the label (section 14.1) concerning:

1. Description of randomization: The sponsor should state that “Randomization was stratified by baseline HbA1c (<8.5% versus \geq 8.5%) and number of prior oral anti-diabetic drug (none versus monotherapy).”
2. In the third paragraph of section 14.1, the sponsor should indicate that at these results were based the analyses using the last observation carried forward (LOCF) method.
3. Subgroup of patients with high baseline (14.1 paragraph 4): this claim was not supported by data. The mean reduction from baseline in A1c were also greater for patients with higher baseline A1c in the placebo group (see review Figure 3.2.4 A-D). The differences between strata were not significant; and the trends of differences between patients stratified using baseline A1c cutoff 8.5 in subgroup analyses (review Figures 4.1.1-4.1.4) varied.
4. Efficacy results of open label arm (14.1, line 648-651): these results are not valid for efficacy claim because of no placebo or active comparator group. As seen in the comment #3 above, the mean reduction from baseline in HbA1c were also greater for patients with higher baseline A1c in the placebo group (see review Figure 3.2.4 A-D).
5. Figure 1 should be a plot of completers.
6. Efficacy data for extension: HbA1c is not a primary endpoint of this study. The interim analysis results listed in the label were not representative because they were based only on a very small portion of the patients enrolled in the study: 10 (6%) in lina 2.5 mg/met 500 mg twice daily group; 10 (4%) in lina 2.5 mg/met 1000 mg twice daily group; and 9 (5%) in met 1000 mg twice daily group. These efficacy data (HbA1c and FPG) should not be included in the label prior to the extension study completion.
7. In Table 7, the upper 95% CI of “Difference from placebo” for Metformin 1000 mg twice daily should be “-0.9”.

2. INTRODUCTION

2.1 Overview

Linagliptin is an inhibitor of DPP-4, an enzyme which rapidly degrades incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thereby increasing insulin release and decreasing the level of glucagon in the circulation in a glucose-dependent manner. Metformin was approved for patients with type 2 diabetes in March 1995, subject of NDA 020357. The efficacy and safety of linagliptin as a monotherapy or as an add-on treatment to other diabetic drugs were reviewed in NDA 201280. The current submission is specifically focused on linagliptin add-on to metformin hydrochloride at fixed dose as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. To support the proposed draft labeling for linagliptin/metformin hydrochloride fixed dose combination tablets, this NDA references the approved US labeling for Glucophage (metformin hydrochloride) tablets.

The applicant submitted data from one phase 2 study 1218.06, four phase 3 studies 1218.17, 1218.18, 1218.20, and the pivotal study 1218.46, and two open-label extension studies 1218.40 and 1218.52. In total, 3084 patients with type 2 diabetes received treatment with linagliptin and metformin; of these, 2585 were treated for at least 24 weeks and 1749 for at least 52 weeks. For the assessment of efficacy and safety, additional supportive non-clinical and clinical studies are cross-referenced to Modules 4 and 5 of NDA 201280 for linagliptin tablets. The phase 3 studies whose results are shown in the sponsor proposed label are marked in the shaded area of Table 2.1.1. Since the data for studies 1218.17, 1218.18, and 1218.20 were reviewed in NDA 201280, the data of the pivotal study 1218.46 (open-label arm excluded) is selected for full statistical review and evaluation in this review.

Table 2.1.1: List of Studies Designed to Assess Safety and Efficacy

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
1218.06	Phase 2 Double-blind placebo-controlled, Met add-on (also include an open-label Glm arm)	12 weeks	Lina 1 mg + Met (65) Lina 5 mg + Met (66) Lina 10 mg + Met (66) PBO + Met (71)	Met failure
1218.17	Phase 3 Double-bind placebo-controlled	24 weeks	Lina 5 mg + Met (523) PBO + Met (177)	Met failure
1218.18	Phase 3 Double-bind placebo-controlled	24 weeks	Lina 5 mg + Met + SU (792) PBO + Met + SU (263)	Met + SU failures
1218.20	Phase 3 Double-bind active-controlled	52 weeks*	Lina 5 mg + Met (778) Glm + Met (781)	Met failures
1218.40	Phase 3 Open-label long-term extension	78 weeks*	Lina 5 mg (2121)	in patients with Type 2 diabetics who continued their treatment from studies 1218.15, 1218.16, 1218.17, and 1218.18
1218.46	Phase 3 Pivotal double-bind placebo-controlled	24 weeks	PBO (72) Lina 2.5 mg+Met 500 mg, twice daily (143) Lina 2.5 mg+Met 1000 mg, twice daily (143) Lina 2.5 mg+Met 1000 mg, twice daily (66)^ Lina 5 mg once daily (142) Met 500 mg twice daily (144) Met 1000 mg twice daily (147)	T2DM patients with insufficient glycaemic control either drug-naïve or treated with one oral antidiabetic agent
1218.52	Phase 3 Double-bind parallel group extension	54 weeks	Lina 2.5 mg + Met 500 mg, twice daily (225) Lina 2.5 mg + Met 1000 mg, twice daily (171) Met 1000 mg, twice daily (170)	Patients who had completed trial 1218.46 and were not being treated with rescue medication

Lina = linagliptin, PBO = placebo, Pio = pioglitazone, Met = metformin (≥ 1500 mg/day or maximum tolerated dose), SU = sulfonylurea (maximum tolerated), Glm= Glimperide (1 to 4 mg/day)

* 104 weeks. On going. Data are available in interim analysis at 52 weeks

^ open-label

2.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. The data were submitted in SAS Xport transport format.

Application:	NDA201281/0000
Company	Boehringer Ingelheim
Drug	Linagliptin
CDER EDR link	\\CDSESUB1\EVSPROD\ NDA201281\0000
Letter date	1/19/2011

The applicant’s electronic submission was well-organized. Parallel structure in the presentation of the results across all studies was well-done and appreciated by the reviewer.

All graphs and tables in the review were created by this reviewer unless otherwise noted.

3. STATISTICAL EVALUATION

3.1. Data and Analysis Quality

I reviewed the quality and integrity of the submitted data. Relevant issues include:

- Whether it is possible to reproduce the primary analysis dataset from tabulation or “raw” datasets : yes
- Whether it is possible to trace how the primary endpoint was derived from the original data source (e.g., case report form): yes.
- Whether it is possible to verify the randomized treatment assignments: yes
- Findings from the Division of Scientific Investigation or other source(s) that question the usability of the data:

Susan Leibenhaut, MD, from the Division of Scientific Investigations requested to verify the following information:

Study 1218.46: the number of treated subjects at the following India sites:

- at site 91004 there are 24 treated subjects
- at site 91015 there are 30 treated subjects.

This reviewer checked the ADSL.xpt and got the following results:

Country=INDIA

Site 91004: 24 (randomized), 28 (safety population), 21 (FAS population), 2 rescued (with sulphonylurea)

Site 91015: 30 (randomized), 33 (safety population), 30 (FAS population), 8 rescued (6 with sulphonylurea and 2 with metformin)

Obs	USUBJID	RESCUE
243	1218-0046-047321	SULPHONYLUREA
713	1218-0046-049642	SULPHONYLUREA
723	1218-0046-049658	SULPHONYLUREA
724	1218-0046-049659	SULPHONYLUREA
762	1218-0046-049776	METFORMIN
764	1218-0046-049778	SULPHONYLUREA
766	1218-0046-049780	SULPHONYLUREA
832	1218-0046-049901	METFORMIN

Therefore the numbers of randomized subjects agree with the number of treated subjects listed in the table.

I did not encounter any problem or difficulty to process the data.

3.2. Evaluation of Efficacy

Study Design and Endpoints

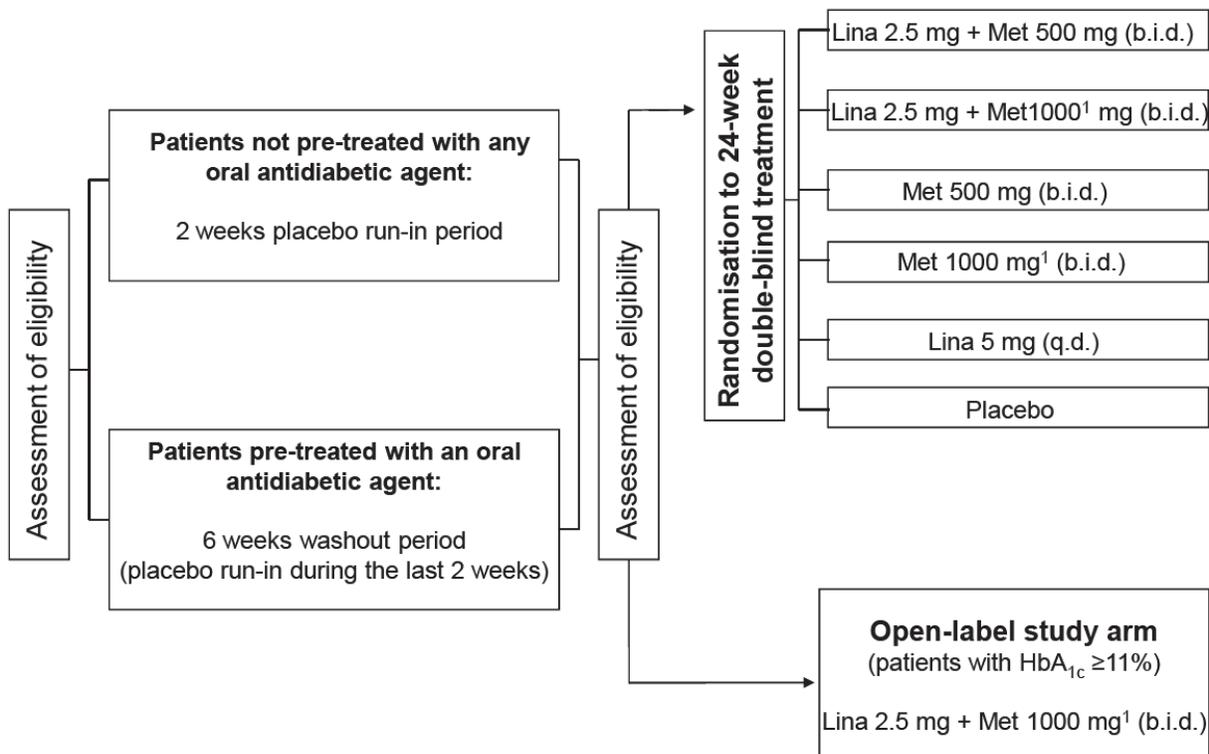
Study 46 is a Phase III randomised, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naïve or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycaemic control.

Study 46 was a multi-national, multi-centre trial with 133 sites in 14 countries (Canada, Croatia, Estonia, France, Germany, India, Lithuania, Mexico, Romania, Russia, Sweden, The Netherlands, Tunisia, and Ukraine)

A total of 1770 patients were enrolled into this study and 792 patients were randomized in a 1:2:2:2:2 ratio to either placebo (72 patients), linagliptin 5 mg (142 patients), metformin 500 mg (144 patients), metformin 1000 mg (147 patients), linagliptin 2.5 mg + metformin 500 mg (143 patients), or linagliptin 2.5 mg + metformin 1000 mg (143 patients). The sample sizes were determined using two-sided t-tests at $\alpha=0.05$, standard deviation and effect size for HbA1c change from baseline to 24 weeks equal to 1.1% and -0.5% (against placebo), and power 0.85. Randomization was stratified by baseline HbA1c (<8.5% versus $\geq 8.5\%$) and number of prior oral anti-diabetic drug (PAD, none versus monotherapy). The main reason for non-randomization was in-/exclusion criteria not met (42.8% of the enrolled patients). All of the randomized patients were treated. The most frequent reasons for discontinuation were due to adverse events (3.3%), refusal to continue trial medication (2.9%), and lack of efficacy (2.3%).

The sponsor's design diagram of the study 1218.46 is shown in Figure 3.2.1.

Figure 3.2.1. Overview of the study design.



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

The primary endpoint for study 1218.46 is the HbA_{1c} change from baseline to 24 weeks. The HbA_{1c} levels were measured at weeks 0, 6, 12, 18, and 24.

The key secondary endpoints (and other endpoints) include the change from baseline in fasting plasma glucose (FPG), occurrence of treat-to-target response (i.e. HbA_{1c} on treatment <7.0% or <6.5%), occurrence of relative efficacy response (i.e. HbA_{1c} lowering by 0.5%), change from baseline in two-hour postprandial glucose (2hPPG) for Meal Tolerance Test (MTT), and the use of rescue medication.

Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.1.

Table 3.2.1. Patient disposition and demographic information

Study population	Placebo	Lina 5 mg Once Daily*	Met 500 mg Twice Daily	Lina 2.5 mg Twice Daily* + Met 500 mg Twice Daily	Met 1000 mg Twice Daily	Lina 2.5 mg Twice Daily* + Met 1000 mg Twice Daily
Randomized	72	142	144	143	147	143
FAS	65 (90%)	135 (95%)	141 (98%)	137 (96%)	138 (94%)	140 (98%)
Per Protocol	63 (87%)	130 (92%)	140 (97%)	133 (93%)	129 (88%)	135 (94%)
Completers	52 (72%)	118 (83%)	120 (83%)	125 (87%)	122 (83%)	129 (90%)
Rescued	19 (26%)	15 (11%)	19 (13%)	10 (7%)	12 (8%)	6 (4%)
Age (yr)						
Mean(SE)	56 (1)	56 (1)	53 (1)	56 (1)	55 (1)	56 (1)
Range	33-78	28-77	30-73	30-80	25-76	26-77
% ≥65 yr	21%	23%	16%	22%	21%	24%
Gender						
% males	50%	56%	57%	51%	53%	54%
Race						
% White	64%	68%	65%	72%	65%	66%
Region						
Africa	4 (6%)	5 (4%)	7 (5%)	7 (5%)	4 (3%)	5 (4%)
Asia	26 (36%)	43 (30%)	49 (34%)	37 (26%)	49 (33%)	45 (31%)
Europe	30 (42%)	73 (51%)	64 (44%)	73 (51%)	70 (48%)	65 (45%)
N. Am*	2 (3%)	7 (5%)	7 (5%)	9 (6%)	7 (5%)	10 (7%)
S. Am^	10 (14%)	14 (10%)	17 (12%)	17 (12%)	17 (12%)	18 (13%)
PAD	38 (53%)	79 (56%)	75 (52%)	76 (53%)	75 (51%)	77 (54%)

*Total daily dose of linagliptin is equal to 5 mg

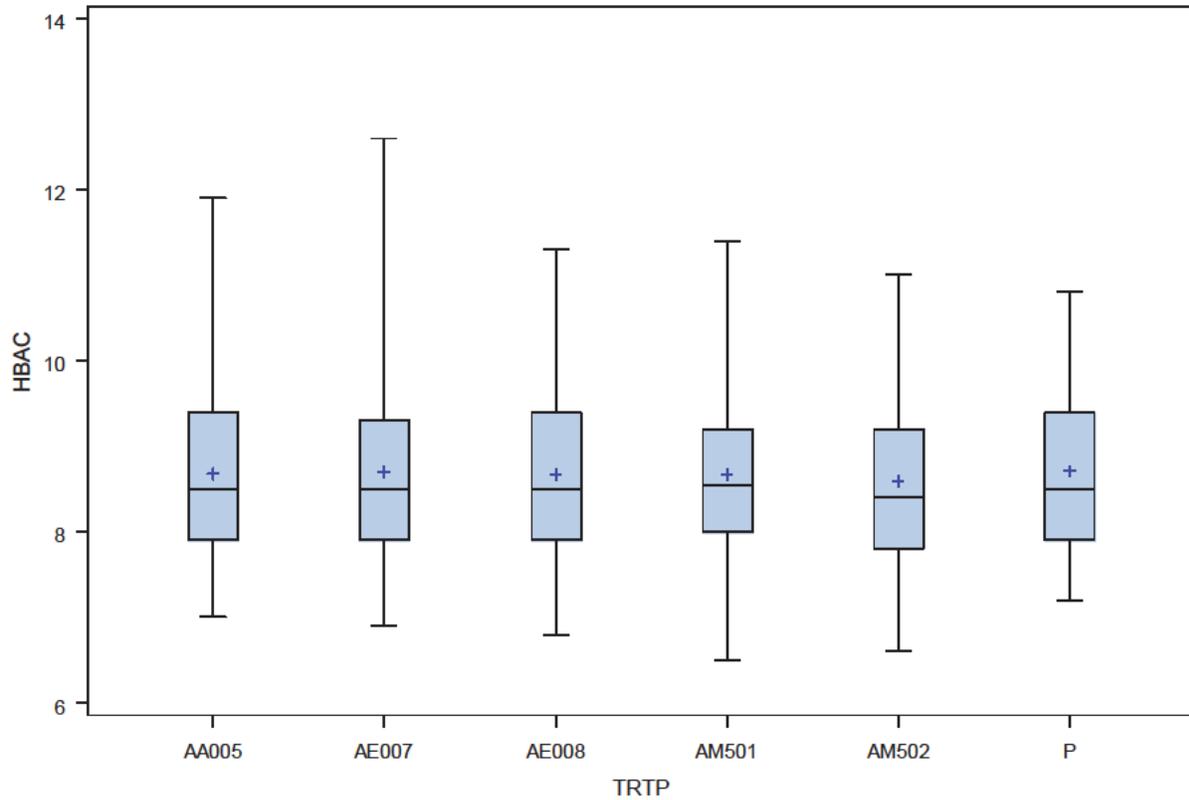
* Canada

^ Mexico

PAD: Previous antidiabetic medication used

The baseline levels of HbA1c in the five double-blind treatment groups are compared in boxplots as shown in Figure 3.2.2. In each boxplot the bottom and top of the box are the 25th and 75th percentile, respectively; the “+” and the line near the middle of the box is the mean and median (50th percentile), respectively; the top line above the box is the maximum observation; and the bottom line below the box is the minimum observation. Across the different treatment groups, the baseline levels of HbA1c appear to have similar means and comparable variability.

Figure 3.2.2. Baseline Levels of HbA1c in Different Treatment Groups.



AA005: Linagliptin 5 mg once daily

AE007: Linagliptin 2.5 mg twice daily + Metformin 500 mg twice daily

AE008: Linagliptin 2.5 mg twice daily + Metformin 1000 mg twice daily

AM501: Metformin 500 mg twice daily

AM502: Metformin 1000 mg twice daily

P: Placebo

Statistical Methodologies

The sponsor's primary analysis is to test the superiority of the combination therapies over the monotherapies in a hierarchical manner with an analysis of covariance (ANCOVA) method with the treatment and previous anti-diabetes therapy as fixed classification effects and baseline HbA1c as linear covariate. The patient population for the primary analysis is the full analysis set (FAS) that was a subset of the treated set including all patients who had a baseline and at least one on-treatment HbA1c measurement available. The last observation carried forward (LOCF) approach was used to replace missing data. This analysis method is adequate for demonstrating efficacy for a combination product.

The sponsor's secondary analysis used ANCOVA (with LOCF) for the continuous variables, and descriptive statistics and logistic regression for the binary response variables. For safety endpoints, the descriptive statistics and Kaplan-Meier analysis were used.

The sponsor imputed data in the following cases: (1) if a patient received rescue medication before measurement of the first on-treatment HbA1c value, the baseline HbA1c value was carried forward; and (2) missing values within a course of measurements on treatment were interpolated based on the last observed value before the missing visit and the first observed value after the missing visit. This reviewer evaluated the datasets and found that in case (1) the number of BOCF was small, therefore the effect of above method on the primary analysis using LOCF can be ignored.

This reviewer's statistical analysis methods have changed slightly from that used in NDA 201280 as specified below. I used LOCF on the sponsor's ANCOVA model as the main imputation method in the primary analysis and in subgroup analysis. The methods for sensitivity analyses were the same as in the review of NDA 201280, that is, I used the per protocol and completers populations for sensitivity analysis. I used MMRM as a secondary analysis with an additional fixed effect 'visit week' to the general model applied to the original dataset. The completers were used for longitudinal graphs.

Results and Conclusions

The superiority of linagliptin and metformin, alone and in combination over placebo was tested for HbA1c change from baseline to week 24 at the level of $\alpha=0.05$ (two-sided) on different analysis populations. The treatment differences between an anti-diabetic drug and placebo, calculated as the adjusted mean change in HbA1c from baseline at Week 24, are summarized in Table 3.2.2 for the primary and sensitivity analyses.

Testing each treatment of anti-diabetic drug(s) over the placebo using FAS with LOCF, the applicant's results suggested significant reduction in HbA1c from the baseline level after 24 weeks treatment. These results were verified by this reviewer using the sponsor's model and method. The (Lina + Met) combinations have larger reductions from placebo in HbA1c levels than that by either component alone, suggesting additional effects from each component drug. Additional efficacy was also seen using three other analysis methods by this reviewer, namely the MMRM method and the two ANCOVA sensitivity analyses using per protocol population and completers populations. However, unlike the results obtained using the FAS population with LOCF, the three analyses by this reviewer revealed that lina 5 mg was not superior over the placebo at the 0.05 level (two-sided).

The results for the secondary endpoint fasting plasma glucose (FPG) compared with placebo are listed in Table 3.2.3. As seen in HbA1c, the additional efficacy of the (Lina + Met) combinations as compared to either component was also observed in the analysis results of FPG using FAS population with LOCF. Again, the three analyses (the MMRM method and the two ANCOVA sensitivity analyses using per protocol population and completers) by this reviewer also revealed

that lina 5 mg was not superior over the placebo at the 0.05 level (two-sided) for the secondary endpoint FPG, different from the results obtained using the FAS population with LOCF.

In summary, the (Lina + Met) combination treatment arms were statistically superior to the placebo and to each corresponding component treatment on both HbA1c and FPG reductions after 24 weeks treatment at a 0.05 level (two-sided).

Table 3.2.2. Glycemic Parameters (HbA1c) at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes

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
Full Analysis Set (LOCF): reported by applicant						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline ¹	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Diff from placebo ¹ (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
achieving A1C <7% (n, %)	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
Full Analysis Set (LOCF): this reviewer's analysis						
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)
Full Analysis Set: this reviewer's analysis (MMRM, Original data)						
Number of patients	n = 64	n = 135	n = 136	n = 137	n = 135	n = 139
Baseline (mean, SE)	8.7 (0.1)	8.7 (0.1)	8.6 (0.1)	8.7 (0.1)	8.5 (0.1)	8.6 (0.1)
Change from baseline ¹ (SE)	-0.3 (0.1)	-0.5 (0.1)	-0.8 (0.1)	-1.3 (0.1)	-1.1 (0.1)	-1.7 (0.1)
Diff from placebo ¹ (95% CI)	--	-0.2 (-0.5, 0.1)	-0.4 (-0.7, -0.1)	-1.0 (-1.3, -0.6)	-0.8 (-1.1, -0.6)	-1.4 (-1.7, -1.1)
Diff from Met alone ¹ (95% CI)				-0.5 (-0.7, -0.3)		-0.5 (-0.8, -0.3)
Diff from Lina alone ¹ (95% CI)				-0.7 (-0.9, -0.5)		-1.2 (-1.4, -0.9)
Completers Analysis Set: this reviewer's analysis (Original data)						
Number of patients	52	118	120	125	122	129
Baseline (mean, SE)	8.7 (0.1)	8.7 (0.1)	8.6 (0.1)	8.7 (0.1)	8.5 (0.1)	8.6 (0.1)
Change from baseline ¹ (SE)	-0.4 (0.1)	-0.5 (0.1)	-0.8 (0.1)	-1.3 (0.1)	-1.2 (0.1)	-1.7 (0.1)
Diff from placebo ¹ (95% CI)		-0.2 (-0.4, 0.1)	-0.4 (-0.7, -0.1)	-0.9 (-1.1, -0.6)	-0.8 (-1.1, -0.6)	-1.3 (-1.6, -1.1)
Diff from Met alone ¹ (95% CI)				-0.5 (-0.7, -0.2)		-0.5 (-0.7, -0.3)
Diff from Lina alone ¹ (95% CI)				-0.7 (-0.9, -0.5)		-1.2 (-1.4, -1.0)
Per Protocol Analysis Set: this reviewer's analysis (Original data)						
Number of patients	51	115	122	122	118	125
Baseline (mean, SE)	8.7 (0.1)	8.7 (0.1)	8.6 (0.1)	8.7 (0.1)	8.5 (0.1)	8.7 (0.1)
Change from baseline ¹ (SE)	-0.4 (0.1)	-0.5 (0.1)	-0.8 (0.1)	-1.3 (0.1)	-1.2 (0.1)	-1.7 (0.1)
Diff from placebo ¹ (95% CI)	--	-0.1 (-0.4, 0.2)	-0.4 (-0.7, -0.1)	-0.9 (-1.2, -0.6)	-0.9 (-1.2, -0.6)	-1.3 (-1.6, -1.0)
Diff from Met alone ¹ (95% CI)				-0.4 (-0.6, -0.2)		-0.4 (-0.7, -0.2)
Diff from Lina alone ¹ (95% CI)				-0.7 (-0.9, -0.5)		-1.2 (-1.4, -1.0)

¹adjusted mean

Table 3.2.3. Glycemic Parameters (Fasting Plasma Glucose) at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes

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
Full Analysis Set (LOCF): reported by applicant						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	203	195	191	199	191	196
Change from baseline ¹ (SE)	10 (5)	-9 (4)	-16 (4)	-33 (4)	-32 (4)	-49 (4)
Diff from placebo ¹ (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)
Full Analysis Set (LOCF): this reviewer's analysis						
Number of patients	61	134	136	135	132	136
Baseline (mean)	203	195	191	199	191	196
Change from baseline ¹ (SE)	10 (5)	-8 (4)	-16 (4)	-33 (4)	-32 (4)	-49 (4)
Diff from placebo ¹ (95% CI)		-18 (-31, -6)	-26 (-38, -13)	-43 (-55, -31)	-42 (-55, -30)	-59 (-72, -47)
<i>Diff from Met alone¹ (95% CI)</i>				-25 (-35, -15)		-41 (-51, -31)
<i>Diff from Lina alone¹ (95% CI)</i>				-17 (-27, -7)		-17 (-27, -7)
Full Analysis Set: this reviewer's analysis (MMRM, Original data)						
Number of patients	59	131	131	133	134	134
Baseline (mean, SE)	199 (7)	193 (4)	191 (4)	195 (5)	190 (5)	195 (5)
Change from baseline ¹ (SE)	-11 (5)	-17 (3)	-25 (3)	-36 (3)	-36 (3)	-51 (3)
Diff from placebo ¹ (95% CI)		-6 (-17, 7)	-14 (-26, -2)	-24 (-36, -12)	-25 (-38, -13)	-39 (-51, -27)
<i>Diff from Met alone¹ (95% CI)</i>				-11 (-20, -1)		-14 (-23, -5)
<i>Diff from Lina alone¹ (95% CI)</i>				-19 (-28, -9)		-34 (-43, -25)
Completers Analysis Set: this reviewer's analysis (Original data)						
Number of patients	46	115	115	118	117	124
Baseline (mean)	199 (7)	193 (4)	189 (4)	195 (5)	188 (5)	195 (5)
Change from baseline ¹ (SE)	-11 (5)	-17 (3)	-26 (3)	-35 (3)	-37 (3)	-50 (3)
Diff from placebo ¹ (95% CI)		-6 (-18, 6)	-14 (-26, -2)	-24 (-36, -11)	-25 (-38, -13)	-39 (-51, -27)
<i>Diff from Met alone¹ (95% CI)</i>				-9 (-19, -0.2)		-13 (-22, -4)
<i>Diff from Lina alone¹ (95% CI)</i>				-17 (-27, -8)		-33 (-42, -24)
Per Protocol Analysis Set: this reviewer's analysis (Original data)						
Number of patients	45	114	118	115	115	120
Baseline (mean, SE)	198 (7)	191 (4)	191 (4)	196 (5)	191 (4)	196 (5)
Change from baseline ¹ (SE)	-12 (5)	-18 (3)	-26 (3)	-36 (3)	-38 (3)	-50 (3)
Diff from placebo ¹ (95% CI)		-6 (-18, 7)	-14 (-26, -2)	-23 (-36, -11)	-26 (-38, -14)	-38 (-50, -26)
<i>Diff from Met alone¹ (95% CI)</i>				-9 (-18, -0.5)		-12 (-21, -3)
<i>Diff from Lina alone¹ (95% CI)</i>				-18 (-27, -9)		-33 (-41, -24)

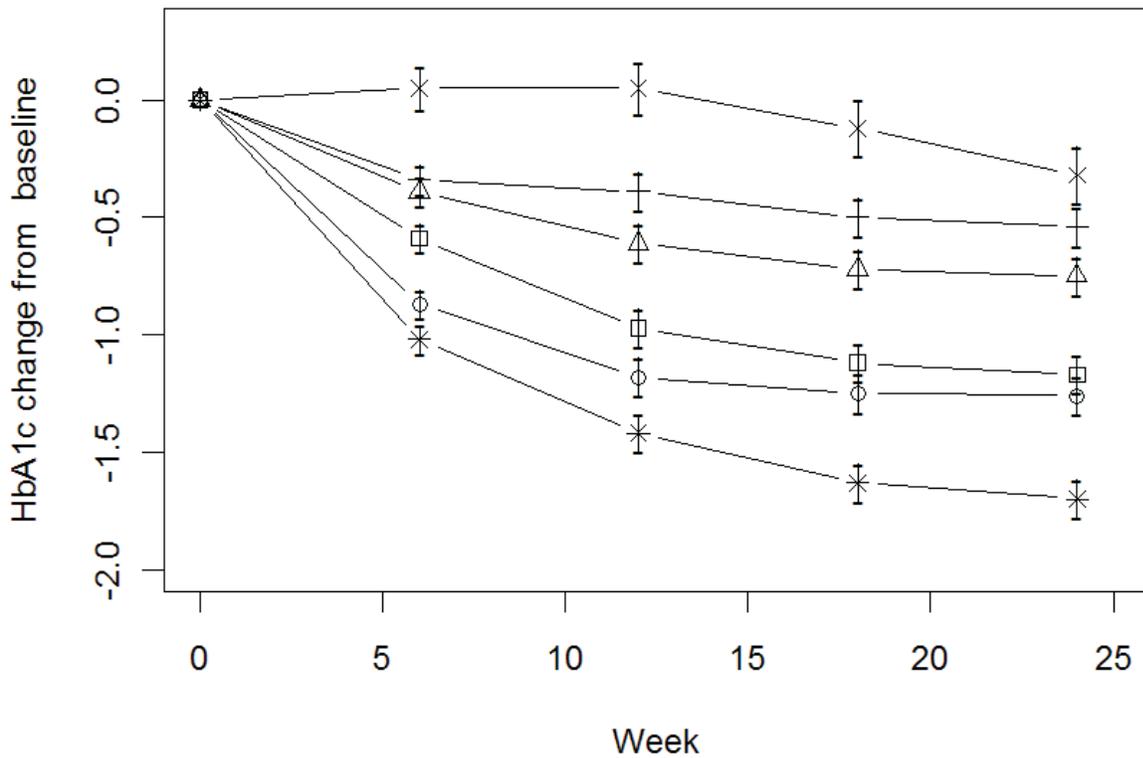
¹ adjusted mean

The time-courses of the completer's HbA1c differences from the baseline with the 95% confidence intervals are shown in Figure 3.2.3.

Figure 3.2.3. HbA1c Changes from Baseline Over 24 Weeks with Linagliptin + Metformin, Alone and in Combination in Study 46.

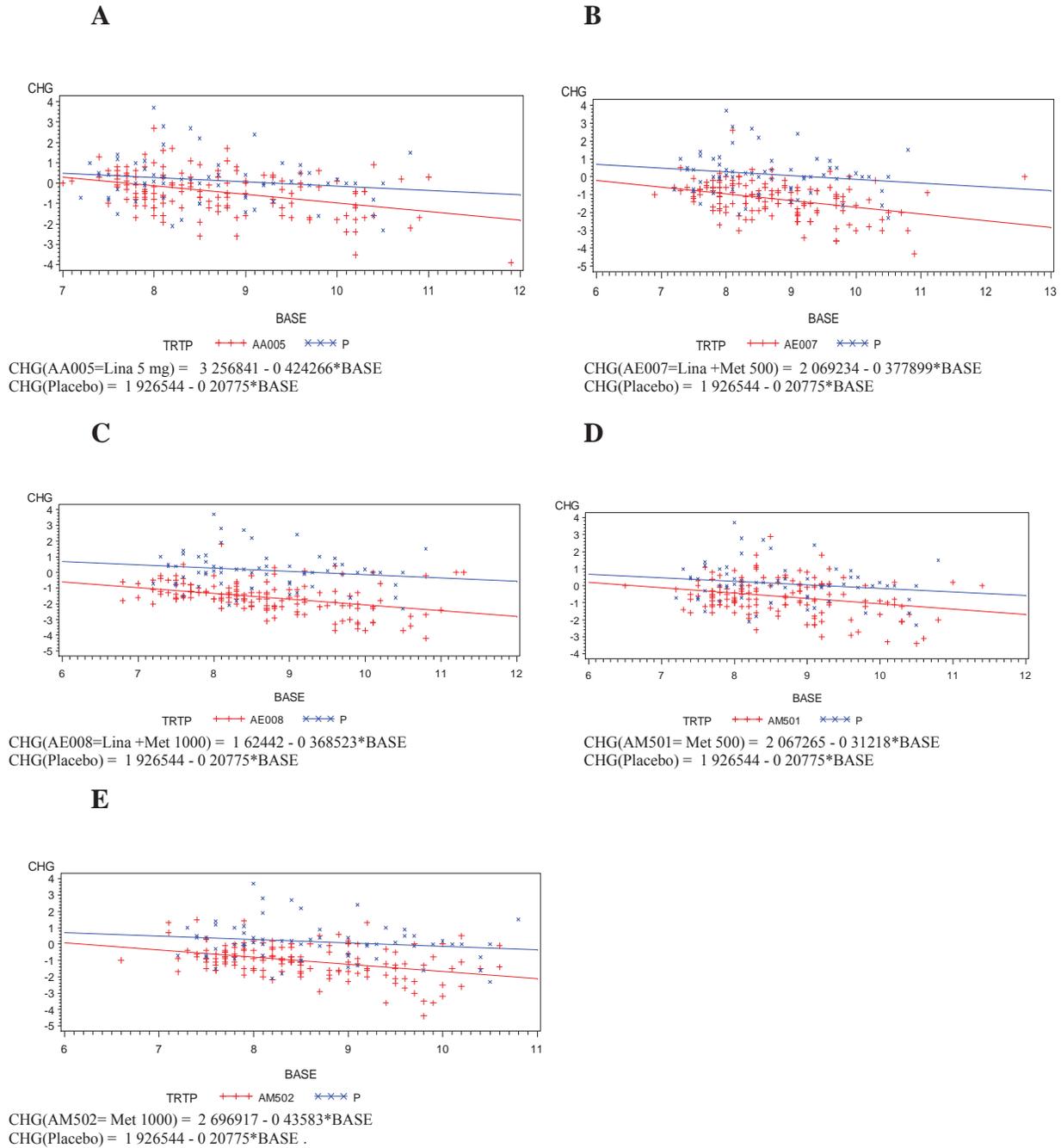
The HbA1c change from baseline denotes the adjust Mean \pm SE.

Treatment: \times matching placebo
 + Linagliptin 5 mg once daily
 \triangle Metformin 500 mg twice daily
 \square Metformin 1000 mg twice daily
 \square Linagliptin 2.5 mg + Metformin 500 mg, twice daily
 $*$ Linagliptin 2.5 mg + Metformin 1000 mg, twice daily



The plots of differences in HbA1c changes from baseline between each single or combined drug and the placebo are shown in Appendix II.

Figure 3.2.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels
A: Linagliptin 5 mg and placebo, B: Metformin 500mg and placebo, C: Linagliptin 2.5 mg+Metformin 500mg and placebo, D: Metformin 1000mg and placebo, and E: Linagliptin 2.5 mg+Metformin 1000mg and placebo, respectively, in Study 46 to Week 24 (LOCF).



This reviewer evaluated the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline as shown in Figure 3.2.4. The treatment-baseline interaction is not significant at alpha=0.10 level for each subplot (A to E) using HbA1c baseline cutoff 8.5% as baseline HbA1c strata in the analysis.

3.3. Evaluation of Safety

There are no significant differences in adverse event rates between each Lina- Met combination and its components as summarized in Table 3.3.1.

Table 3.3.1. List of Adverse Events by Treatments on All Randomized Patients with Type 2 Diabetes

The number of subjects were those with at least one adverse event.

Treatment	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Total, n (%)
Lina 2.5 mg + Met 500 mg Twice Daily, n=143	65 (45%)	33 (23%)	4 (3%)	76 (53%)
Lina 5 mg Once Daily, n=142	69 (49%)	32 (23%)	1 (1%)	82 (58%)
p-value (2-sided)	0.596	0.913	0.178	0.435
Lina 2.5 mg + Met 500 mg Twice Daily, n=143	65 (45%)	33 (23%)	4 (3%)	76 (53%)
Met 500 mg Twice Daily, n=144	67 (47%)	39 (27%)	0 (0%)	83 (58%)
p-value (2-sided)	0.855	0.434	0.043	0.444
Lina 2.5 mg + Met 1000 mg Twice Daily, n=143	77 (54%)	30 (21%)	4 (3%)	88 (62%)
Lina 5 mg Once Daily, n=143	69 (48%)	32 (22%)	1 (1%)	82 (57%)
p-value (2-sided)	0.344	0.774	0.176	0.470
Lina 2.5 mg + Met 1000 mg Twice Daily, n=143	77 (54%)	30 (21%)	4 (3%)	88 (62%)
Met 1000 mg Twice Daily, n=147	66 (46%)	34 (24%)	5 (3%)	81 (55%)
p-value (2-sided)	0.193	0.570	0.735	0.266

In addition to the analyses on adverse events, this reviewer investigated the laboratory data for any safety signs caused by each combination (Lina+Met) which were worse significantly than that by one or both of its components at organ levels. Tables 3.3.2 and 3.3.3 list those variables of laboratory assays which showed each combination (Lina+Met) to be significantly worse than at least one component at the indicated visit.

Table 3.3.2. List of Laboratory Assays That Were Significantly Worse on Patients Treated by Lina 2.5 mg + Met 500 mg Twice Daily Versus At Least One Component

A: Lina 2.5 mg + Met 500 mg Twice Daily

Test	visit	A mean (95% CI)	B mean (95% CI)	A-B (95% CI)	p-value
B: Lina 5 mg Once Daily					
Leukocytes	5	7.60 (7.23, 7.96)	7.17 (6.88, 7.44)	0.43 (-0.02, 0.89)	0.062
Alkaline phosphatase	3	85.4 (81.1, 89.6)	79.6 (75.7, 83.4)	5.8 (0.1, 11.5)	0.046
Erythrocytes	998	4.83 (4.75, 4.90)	4.95 (4.87, 5.03)	-0.12 (-0.23, -0.02)	0.024
B: Met 500 mg Twice Daily					
Aspartate transaminase	998	26.3 (22.7, 29.9)	22.4 (20.8, 24.0)	3.9 (0.01, 7.8)	0.049
CK_MB	3	5.69 (2.94, 8.44)	2.82 (2.00, 3.64)	2.87 (0.21, 5.53)	0.036
Neutrophils	5	60.8 (59.3, 62.2)	57.6 (56.1, 59.1)	3.2 (1.1, 5.3)	0.003
Urea	998	5.34 (5.05, 5.62)	4.92 (4.53, 5.00)	0.42 (0.04, 0.80)	0.031

Visit 3: treatment day 1 (Study Week 0 after randomization)

Visit 5: treatment day 96 (study Week 12)

Visit 998: day 181 (post-treatment period, study Week 25)

Table 3.3.3. List of Laboratory Assays That Were Significantly Worse on Patients Treated by Lina 2.5 mg + Met 1000 mg Twice Daily Versus At Least One Component

A: Lina 2.5 mg + Met 1000 mg Twice Daily

Test	visit	A mean (95% CI)	B mean (95% CI)	A-B (95% CI)	p-value
B: Lina 5 mg Once Daily					
Calcium	998	2.42 (2.40, 2.44)	2.39 (2.37, 2.40)	0.03 (0.003, 0.057)	0.032
Erythrocytes	998	4.82 (4.74, 4.90)	4.95 (4.87, 5.03)	-0.13 (-0.24, -0.01)	0.027
Urine ketones	3	0.079 (0.031, 0.126)	0.014 (-0.002, 0.030)	0.065 (0.015, 0.115)	0.012
Urine leukocytes	3	6.37 (3.30, 9.44)	2.87 (1.54, 4.20)	3.50 (0.13, 6.87)	0.042
Amylase	5	73.1 (66.3, 79.8)	62.3 (56.5, 68.0)	10.8 (1.90, 19.6)	0.017
	998	74.7 (67.6, 81.7)	60.4 (54.2, 66.6)	14.3 (4.9, 23.7)	0.003
Leukocytes	5	7.66 (7.34, 7.98)	7.16 (6.88, 7.44)	0.5 (0.08, 0.92)	0.02
B: Met 1000 mg Twice Daily					
Neutrophils	5	61.1 (59.8, 62.3)	56.8 (55.4, 58.3)	4.23 (2.31, 6.16)	<0.0001
	998	60.4 (58.7, 62.0)	58.0 (56.6, 59.4)	2.38 (0.19, 4.56)	0.033
Urine leukocytes	3	6.37 (3.30, 9.44)	2.59 (1.82, 3.36)	3.78 (0.66, 6.89)	0.018

Visit 3: treatment day 1 (Study Week 0 after randomization)

Visit 5: treatment day 96 (study Week 12)

Visit 998: day 181 (post-treatment period, study Week 25)

Above results appear to suggest significant elevations in some immune system reactions in patients treated by the combined Lina+Met drugs versus those by the component drugs.

3.4 Benefit:Risk Assessment (Optional)

No benefit:risk analysis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Efficacy analyses are performed across subgroups by sex, age (<65 years, ≥65 years), race (Caucasian, others), region (Asia, Europe, other regions – because of only small number of patients in the US), usage of previous anti-diabetic drugs (Yes, No), baseline HbA1c level for randomization stratification (<8.5%, ≥8.5%), baseline BMI (<30 Kg/m², ≥30 Kg/m²), baseline eGFR (≥90 mL/min, <90 mL/min), and the outcome of rescue status during treatment (Yes, No). The LOCF approach was used for dealing with missing values. The results are shown in forest plots for each combination (Lina+Met) versus its components.

Forest plots for each combined drug versus its components. Results were from ANCOVA analyses using LOCF method.

Figure 4.1.1. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 2.5 mg+Metformin 1000mg Twice Daily and Linagliptin 5 mg Once Daily Treatments in Study 46 at Week 24.

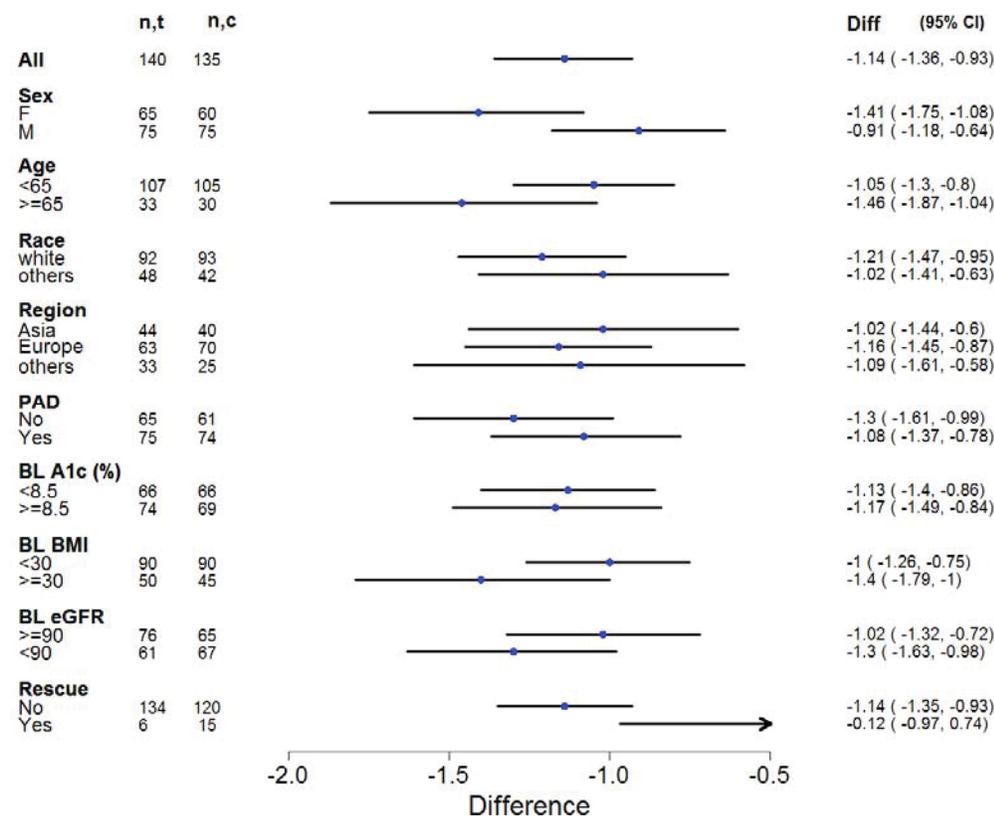


Figure 4.1.2. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 2.5 mg+Metformin 1000mg Twice Daily and Metformin 1000mg Twice Daily Treatments in Study 46 at Week 24.

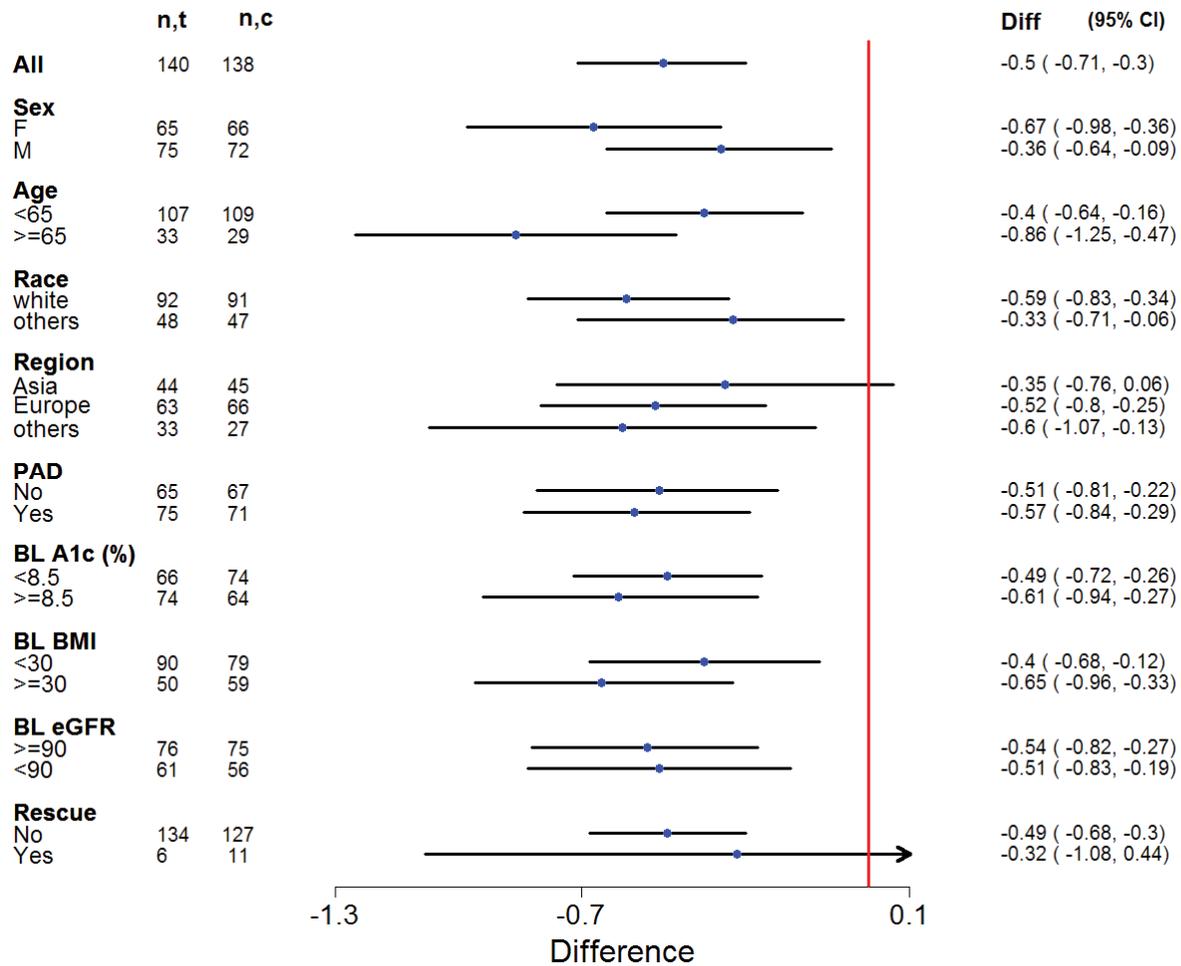


Figure 4.1.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 2.5 mg+Metformin 500mg Twice Daily and Linagliptin 5 mg Once Daily Treatments in Study 46 at Week 24.

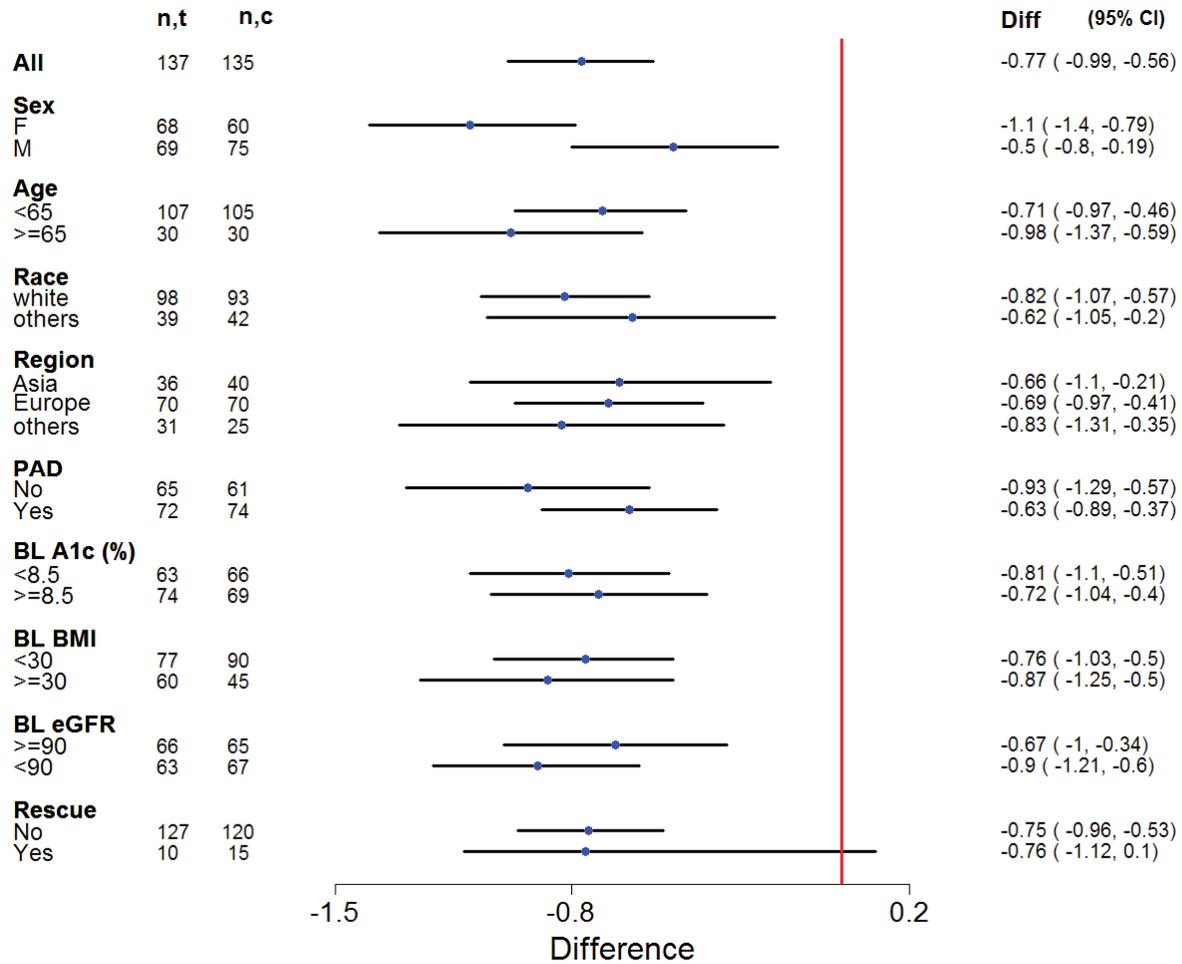
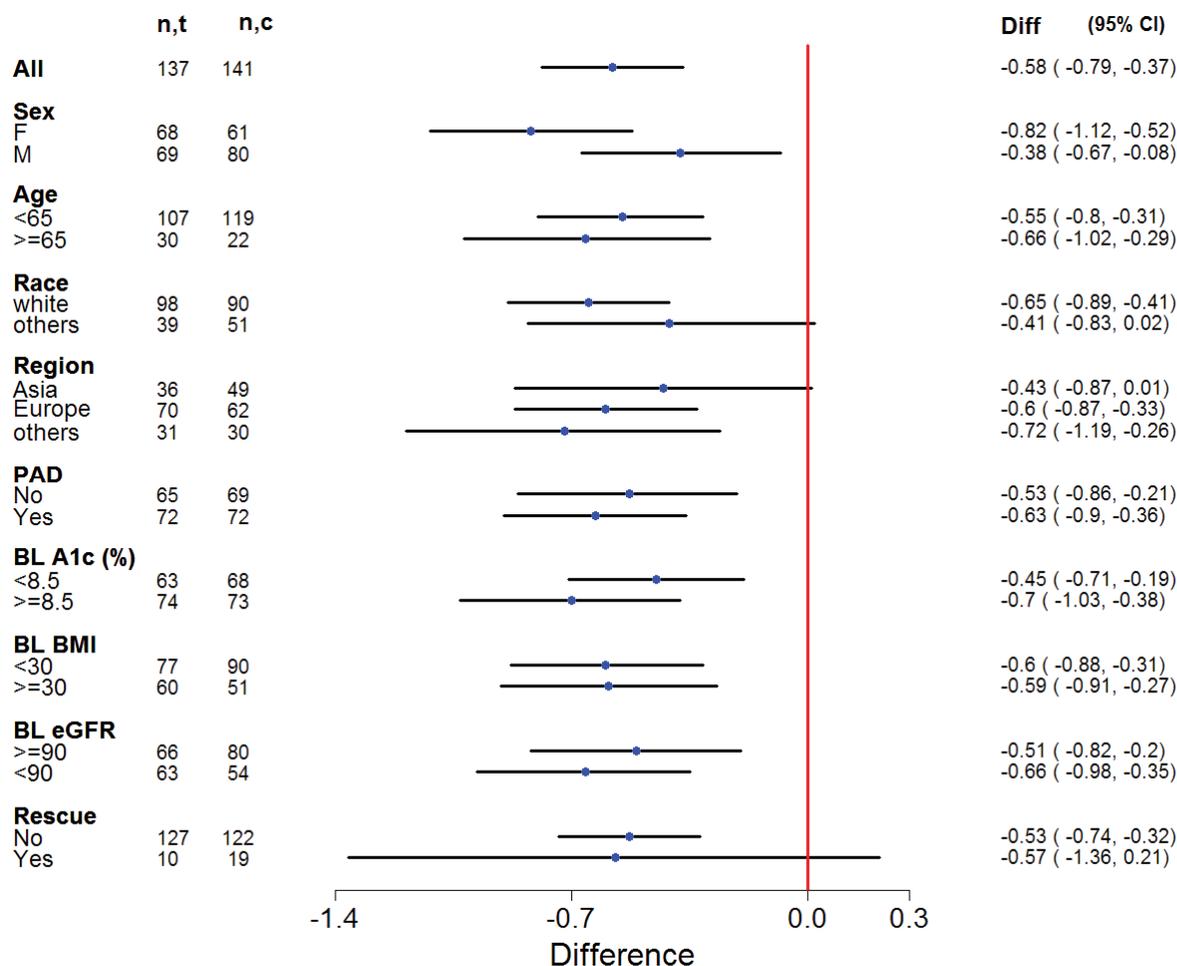


Figure 4.1.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 2.5 mg+Metformin 500mg Twice Daily and Metformin 500mg Twice Daily Treatments in Study 46 at Week 24.



The forest plots for each drug treatment versus placebo are in Appendix III.

Superiority of each combination (Lina+Met) over its components is supported across subgroups based on the changes of HbA1c.

The above results of subgroup analyses suggest that females derive greater benefit from adding either Lina or Met to the other drug than do males. In particular, the treatment-by-sex interaction p-values comparing (Lina+Met) to Met alone were 0.0363 and 0.1264 for metformin 500 mg (twice daily) and 1000 mg (twice daily), respectively. I looked to see if this pattern was also seen in the original application NDA 201280 studies 17 and 18 which compared the Lina+Met combination to Met. Treatment differences were numerically greater for females than they were for males in both studies. However, the treatment-by-sex interaction p-values were not significant, equal to 0.43 and 0.23 for studies 17 and 18, respectively. From a statistical

standpoint, the data across the two NDAs were not sufficiently compelling to conclude, in patients already receiving metformin, that females derived a greater benefit from adding linagliptin than did males. Similarly, no consistent difference by gender was seen in studies comparing Lina monotherapy versus placebo in this application and NDA 201280 studies 16 and 50.

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This statistical review covers the pivotal randomized trial of co-administered linagliptin and metformin (Study 46). Other (lina + met) combination trials submitted by the sponsor (Studies 17, 18, and 20) were reviewed in NDA 202180, the original submission for linagliptin, therefore were not reviewed as part of the current submission.

The results of study 1218.46 (see Table 1 below) support the efficacy of linagliptin add-on to metformin hydrochloride at fixed dose as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus after 24 weeks of treatment based HbA1c reduction. Particularly, the combination treatment is statistically superior to the placebo and to each corresponding component treatment after 24 weeks treatment at a 0.05 level (two-sided). The results from the sensitivity analyses (such as MMRM, completers, and per protocol) and key secondary endpoint, fasting plasma glucose level, support the superior of the combination to the placebo and to each corresponding component treatment on both HbA1c and FPG reductions after 24 weeks treatment at a 0.05 level (two-sided). These efficacy results were supported by the data of studies 17 and 20 which were reviewed in NDA 201280.

The dropout rates by treatment group in study 46 range from 10% to 28%. The largest dropout rate (28%) occurred in the placebo group. The dropout rates in the combination (Lina+Met) groups and the corresponding lina and met components are a little lower, from 10% to 17%. The dropout rates are not very large and therefore they are not a concerning issue for the efficacy conclusion.

Note that the superiority of linagliptin 5 mg over placebo was supported by data from NDA 201280 study 16 and study 50. However, in the current submission, although not critical for the efficacy claims of study 46, linagliptin 5 mg daily did not show superiority over placebo after 24 weeks treatment at a 0.05 level (two-sided) using efficacy analyses other than the LOCF approach. The estimated treatment differences for HbA1c were -0.1 or -0.2. These smaller treatment differences compared to LOCF results were due primarily to differences in the estimated changes from baseline in the placebo group which were much lower (i.e., greater improvement) in the sensitivity analyses. The sensitivity analyses must be considered in the light of recent criticism of LOCF. Also, the percentages of 7% HbA1c responders (Table 1.1)

for placebo and linagliptin based on LOCF population were identical (10.8% vs 10.4%) raising questions about the efficacy of linagliptin 5 mg QD in this trial.

Subgroup analyses suggest that females derive greater benefit from adding either Lina or Met to the other drug than do males.

There are no significant differences in adverse event rates between each Lina- Met combination and its components. Laboratory assays suggest significant elevations in some immune system reactions in patients treated by the combined Lina+Met drugs versus those by the component drugs.

Table 1. Glycemic Parameter HbA1c at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes (LOCF)

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)

5.2 Conclusions and Recommendations

Confirmation of efficacy: The results of the pivotal study 1218.46 support the efficacy of linagliptin add-on to metformin hydrochloride at fixed dose as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus after 24 weeks of treatment based HbA1c reduction. Particularly, the combination treatment is statistically superior to the placebo and to each corresponding component treatment after 24 weeks treatment at a 0.05 level (two-sided).

Table 1. Glycemic Parameter HbA1c at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes (LOCF)

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)

<i>Diff from Lina alone¹ (95% CI)</i>				-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)

The results from the sensitivity analyses (such as MMRM, completers, and per protocol) and key secondary endpoint, fasting plasma glucose level, support the superiority of the combination to the placebo and to each corresponding component treatment on both HbA1c and FPG reductions after 24 weeks treatment at a 0.05 level (two-sided).

Subgroup analyses suggest that females derive greater benefit from adding either Lina or Met to the other drug than do males.

There were no significant differences in adverse event rates between each Lina- Met combination and its components. Laboratory assays suggest significant elevations in some immune system reactions in patients treated by the combined Lina+Met drugs versus those by the component drugs.

The results from non-LOCF analysis methods (this reviewer’s MMRM, completers, and per protocol) showed that linagliptin 5 mg was not statistically superior to placebo at the 0.05 alpha level (two-sided). It is, however, not critical to the determination of efficacy of the combinations (Lina+Met) since the determination does not require efficacy data from placebo and the data from linagliptin monotherapy is used only to support the efficacy of metformin in the combination. Nevertheless the efficacy of linagliptin monotherapy needs to be considered in the context of the submission.

5.3 Labelling Comments

ref. Sponsor’s Proposed Labeling section 14.1

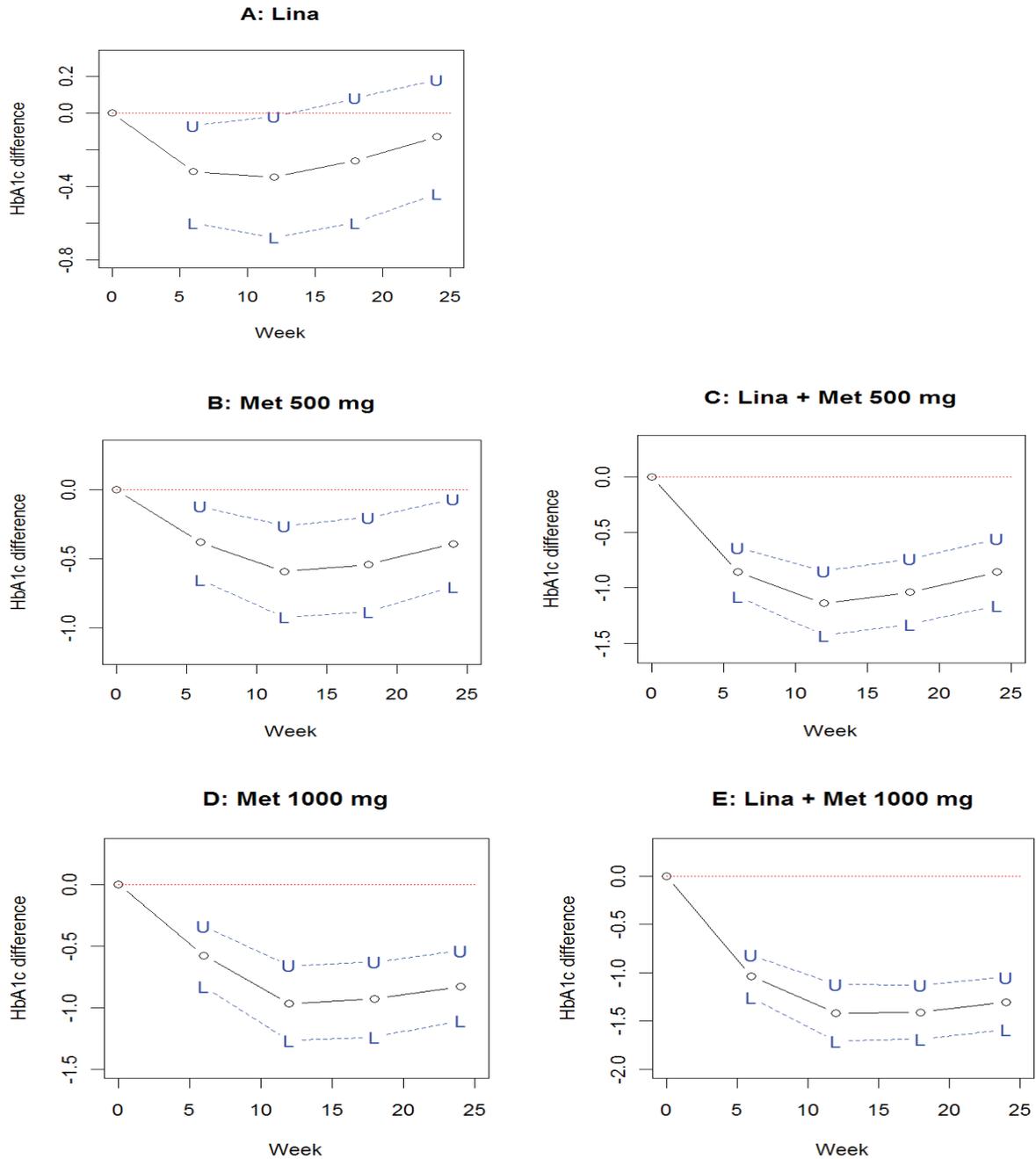
The statistical review addresses statements in the label (section 14.1) concerning:

8. Description of randomization: The sponsor should state that “Randomization was stratified by baseline HbA1c (<8.5% versus ≥8.5%) and number of prior oral anti-diabetic drug (none versus monotherapy).”
9. In the third paragraph of section 14.1, the sponsor should indicate that at these results were based the analyses using the last observation carried forward (LOCF) method.
10. Subgroup of patients with high baseline (14.1 paragraph 4): this claim was not supported by data. The mean reduction from baseline in A1c were also greater for patients with higher baseline A1c in the placebo group (see review Figure 3.2.4 A-D). The differences between strata were not significant; and the trends of differences between patients stratified using baseline A1c cutoff 8.5 in subgroup analyses (review Figures 4.1.1-4.1.4) varied.

11. Efficacy results of open label arm (14.1, line 648-651): these results are not valid for efficacy claim because of no placebo or active comparator group. As seen in the comment #3 above, the mean reduction from baseline in HbA1c were also greater for patients with higher baseline A1c in the placebo group (see review Figure 3.2.4 A-D).
12. Figure 1 should be a plot of completers.
13. Efficacy data for extension: HbA1c is not a primary endpoint of this study. The interim analysis results listed in the label were not representative because they were based only on a very small portion of the patients enrolled in the study: 10 (6%) in lina 2.5 mg/met 500 mg twice daily group; 10 (4%) in lina 2.5 mg/met 1000 mg twice daily group; and 9 (5%) in met 1000 mg twice daily group. These efficacy data (HbA1c and FPG) should not be included in the label prior to the extension study completion.
14. In Table 7, the upper 95% CI of “Difference from placebo” for Metformin 1000 mg twice daily should be “-0.9”.

APPENDIX I. Time courses of HbA1c Changes from Baseline between active treatments and placebo.

Figure 1. The Plot of HbA1c Changes from Baseline between A: Linagliptin 5 mg once daily and placebo, B: Metformin 500mg twice daily and placebo, C: Linagliptin 2.5 mg+Metformin 500mg, twice daily and placebo, D: Metformin 1000mg twice daily and placebo, and E: Linagliptin 2.5 mg+Metformin 1000mg, twice daily and placebo in Study 46 to Week 24.



APPENDIX II. Forest Plots of HbA1c Changes from Baseline Between active Treatments and Placebo in Subgroups at Week 24.

Forest plots for each combined drug versus its components. Results were from ANCOVA analyses using LOCF method.

Figure 1. The Forest Plot of HbA1c Changes from Baseline between Linagliptin 5 mg and placebo in Subgroups at Week 24.

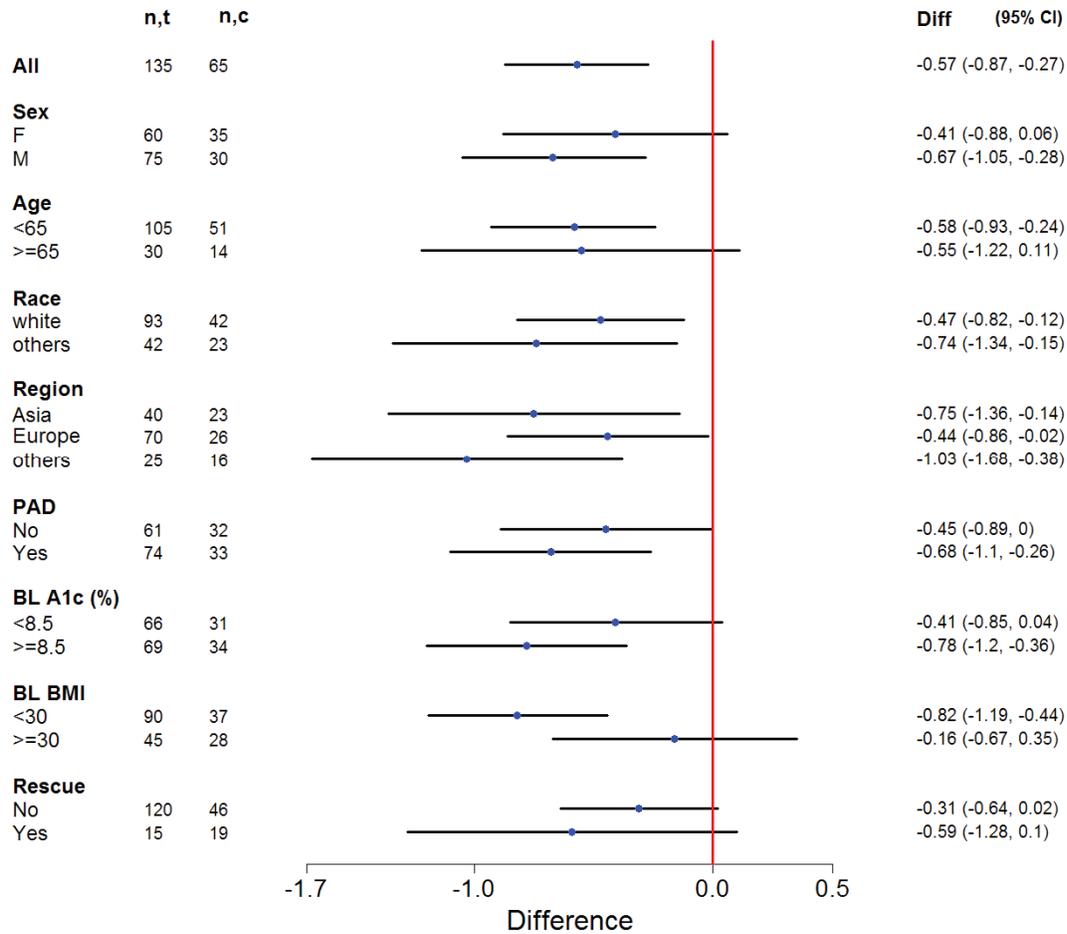


Figure 2. The Forest Plot of HbA1c Changes from Baseline between Linagliptin 2.5 mg+Metformin 500 mg Twice Daily and placebo in Subgroups at Week 24.

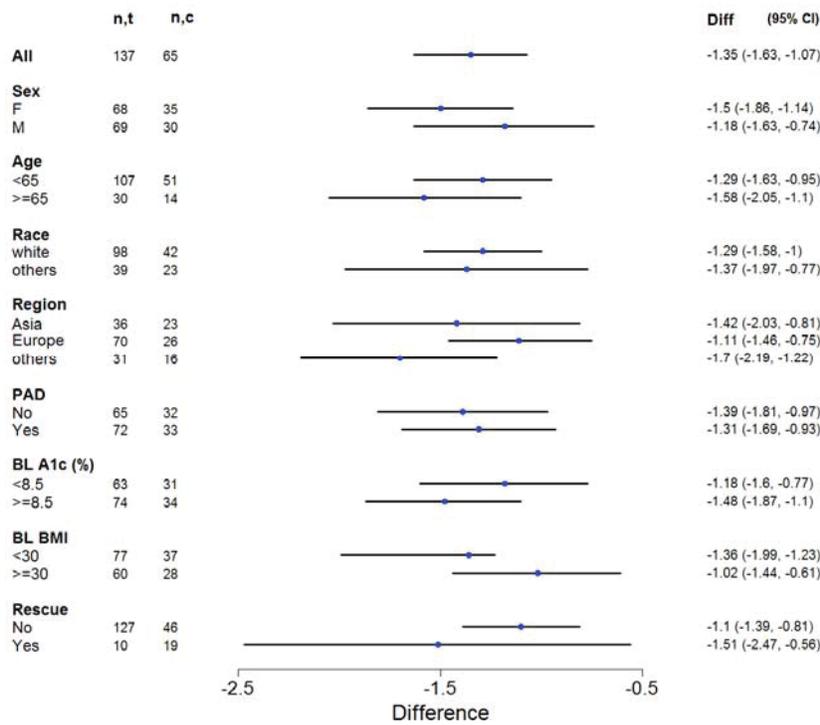


Figure 3. The Forest Plot of HbA1c Changes from Baseline between Linagliptin 2.5 mg+Metformin 1000 mg Twice Daily and placebo Treatments in Subgroups at Week 24.

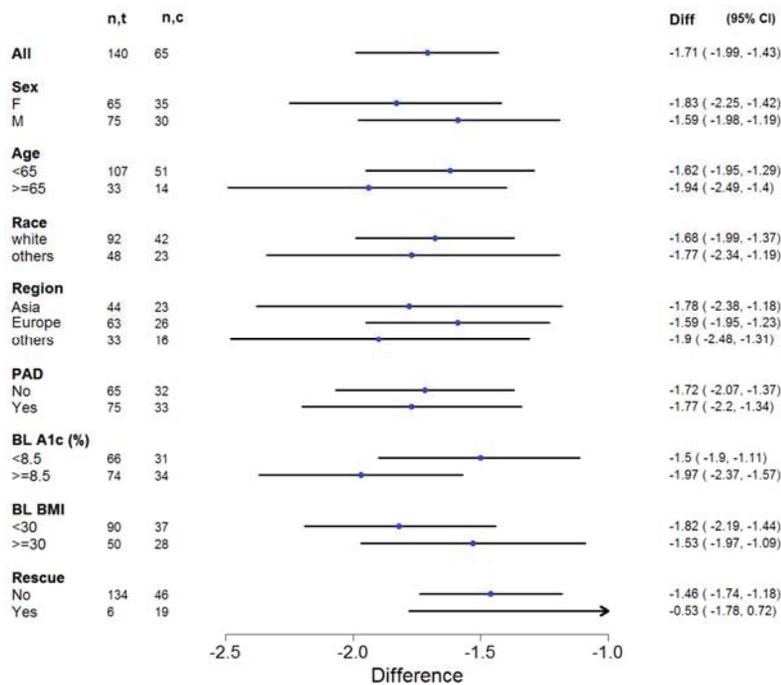


Figure 4. The Forest Plot of HbA1c Changes from Baseline between Metformin 500 mg Twice Daily and placebo Treatments in Subgroups at Week 24.

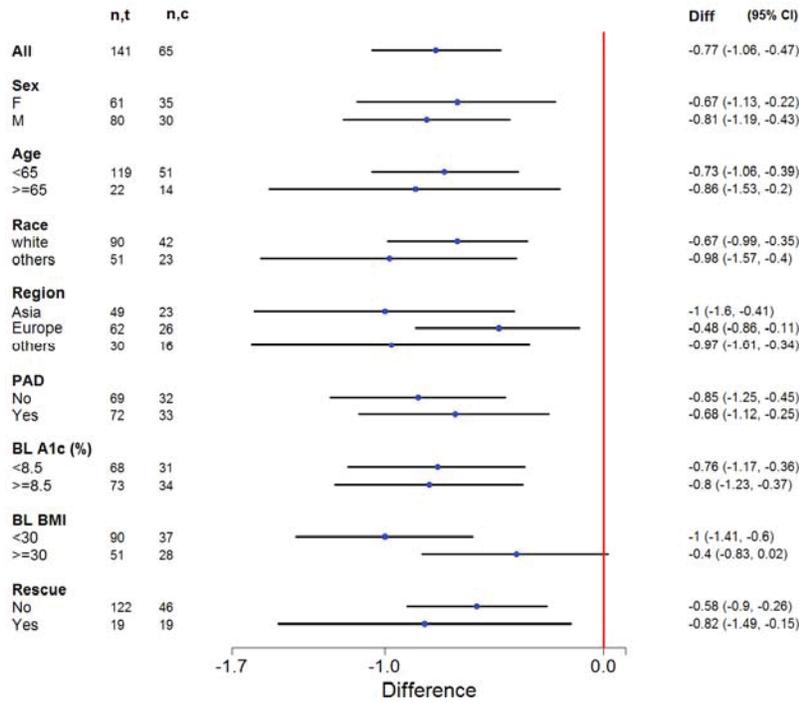
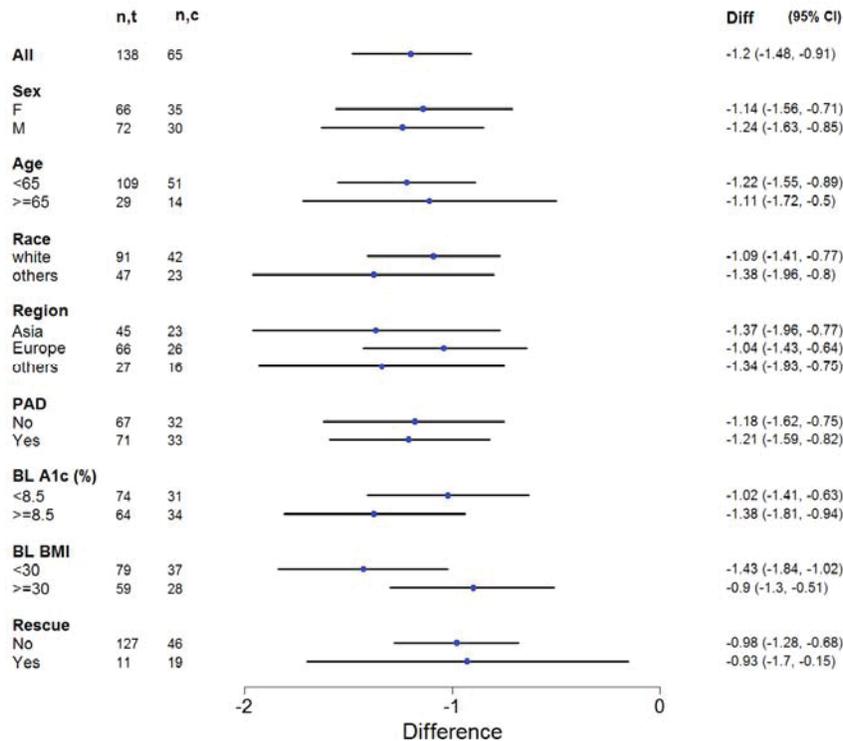


Figure 3.1.3. The Forest Plot of HbA1c Changes from Baseline between Metformin 1000 mg Twice Daily and placebo Treatments in Subgroups at Week 24.



SIGNATURES/DISTRIBUTION LIST (Optional)

Primary Statistical Reviewer:

Date:

Concurring Reviewer(s):

Statistical Team Leader:

Biometrics Division Director:

cc:

Project Manager

Medical Officer

Medical Team Leader

Primary Statistical Reviewer

Statistical Team Leader

Biometrics Division Director

Lillian Patrician

c:\NDA\statreview.doc

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial:

Protocol Number (s): 1218.46

Protocol Title (optional): A phase III randomised, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of BI 1356 2.5 mg + metformin 500 mg, or of BI 1356 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily), and BI 1356 (5.0 mg, once daily) over 24 weeks in drug naïve or previously treated (4 weeks wash-out and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycaemic control

Phase: 3

Control: Placebo/Active Control

Blinding: Double-Blind/Open-Label

Number of Centers:

Region(s) (Country):

Duration: 24 Weeks

Treatment Arms: Placebo/ AA005/AE007/AE008/AM501/AM502/AE300

Treatment Schedule:

Randomization: Yes/No

Ratio: 1:2:2:2:2

Method of Randomization:

If stratified, then the Stratification Factors: PAD, A1c cutoff 8.5%

Primary Endpoint: (change from baseline in A1c)

Primary Analysis Population: (mITT)

Statistical Design: Superiority

(If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data?)

Margin =

%Retained =)

Adaptive Design: Yes/No

Primary Statistical Methodology: ANCOVA

Interim Analysis: Yes/No

If yes:

No. of Times:

Method:

α Adjustment:

α Spending Function:

DSMB:

Sample Size: 72, 144, 144, 144, 144

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

Statistic =

Power >0.88

Δ=

Lina 2.5 mg plus metformin 500 mg, twice daily vs. Lina 5 mg daily: -0.8%

Lina 2.5 mg plus metformin 1000 mg, twice daily vs. Lina 5 mg daily: -1.0%

Lina 2.5 mg plus metformin 500 mg, twice daily vs. metformin 500 mg twice daily: -0.5%

Lina 2.5 mg plus metformin 1000 mg, twice daily vs. metformin 1000 mg twice daily: -0.5%

Lina 5 mg daily vs. placebo: -0.5%

metformin 500 mg twice daily vs. placebo: -0.8%

metformin 1000 mg twice daily vs. placebo: -1.0%

α = 0.05

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? Yes
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? LOCF
- Was there a **Multiplicity** involved? No
If yes,
Multiple Arms (Yes/No)?
Multiple Endpoints (Yes/No)?
Which method was used to control for type I error?
- **Multiple Secondary Endpoints:** Are they being included in the label? No. (If yes, method to control for type 1 error.)

Were Subgroup Analyses Performed (Yes/No)? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report?
No
- Overall, was the study positive (Yes/No)? Yes

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

/s/

WEI LIU
10/17/2011

JON T SAHLROOT
10/17/2011
concur

STATISTICS FILING CHECKLIST FOR NDA/BLA

NDA Number: 201281

Applicant: Boehringer Ingelheim

Stamp Date: 1/19/2011

Drug Name: Linagliptin

NDA/BLA Type: New NDA

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			For efficacy and in some trials for safety
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			LOCF method

STATISTICS FILING CHECKLIST FOR NDA/BLA

Summary of trials to support efficacy

Study	Treatments	Duration	Center (countries)	n
1218-46 pivotal	Lina 5 mg + Met Lina 2.5 + Met Lina 5 mg PBO Met	24-WK	133 (14)	286 66 142 72 291
1218-06 under review in NDA201280	Lina 1 mg +Met Lina 5 mg + Met Lina 10 mg+Met PBO Glimepiride*	12-WK	47 (6)	70 64 62 66 64
1218-17 under review in NDA201280	Lina + Met Met	24-WK	82 (10)	524 177
1218-18 under review in NDA201280	Lina + Met+SU Met+SU	24-WK	100 (11)	778 262
1218-20^ under review in NDA201280	Lina + Met Glimepiride + Met	52-WK	209 (16)	779 781
1218-40 EXT	Lina +Met	78-WK	Countries from Trial 1218.17	611
1218-52 EXT	Lina + Met Met	54-WK	Countries from Trial 1218.46	396 171

Lina=linagliptin, PBO=placebo, Met=metformin, SU=sulfonylurea

* Open-label

^ NI margin 0.35%

Wei Liu

03/1/2010

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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

/s/

WEI LIU
03/08/2011

JON T SAHLROOT
03/08/2011