CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201280Orig1s000

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/Serial Number:	201-280 / SN 000
Drug Name:	Tardjenta [1] (Linagliptin, BI 1356)
Indication(s):	Treatment of patients with type 2 diabetes mellitus
Applicant:	Boehringer Ingelheim Pharmaceuticals Inc
Date(s):	Submitted July 2, 2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Xiao Ding, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D. Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer: Somya (Verma) Dunn, M.D. Medical Team Leader: Ilan Irony, M. D.
Project Manager:	Raymond Chiang, M.S. (DMEP)

Keywords: clinical studies, cardiovascular safety, meta-analysis

[1] At the time of filing of this review, the trade name under review is Tardjenta, but DMEPA has not reached a decision on the adequacy of such trade name.

Table of Contents

1 Executive Summary 5
1.1 Conclusions and Recommendations 5
1.2 Brief Overview of Clinical Studies 6
1.3 Statistical Issues and Findings 6
2 Introduction 8
2.1 Product Description 8
2.2 Clinical Trial Overview 8
2.3 Data Sources 8
3 Statistical Evaluation 9
3.1 Evaluation of Safety 9
3.1.1 Study Designs 9
3.1.2 Statistical Methodologies 11
3.1.2.1 Methods of Imputing Missing 11
3.1.2.2 Analysis of Event Incidence 12
3.1.2.3 Time-to-Event Analysis 12
3.1.2.4 Handling of Trials with zero events 12
3.1.3 Populations 13
3.1.4 Subject Disposition, Demographic and Baseline Characteristics 15
3.1.5 Endpoints 20
3.1.5.1 Primary Composite Endpoints 20
3.1.5.2 Secondary Endpoints 20
3.1.6 Results and Conclusions 21
3.1.6.1 Primary Composite Endpoint 21
3.1.6.1.1 Analysis of Incidence 21
3.1.6.1.2 Sensitivity Analyses of Incidence 22
3.1.6.1.3 Forest Plot of All Results for Primary Composite Endpoint 24
3.1.6.1.4 Time-to-Event Analysis of Primary composite endpoint 25
3.1.6.1.5 Sensitivity Time-to-Event Analyses 26
3.1.6.2 Secondary Endpoint 28
4 Findings in Special/Subgroup Populations 32
4.1 Gender, Race, and Age 32
4.2 Other Special/Subgroup Populations 33
4.2.1 Ethnicity 33
4.2.2 Baseline BMI 34
4.2.3 Baseline Renal Impairment Status 34
4.3 Summary Forest Plot for all Subgroup Analysis Results 34
5 Summary and Conclusions 35
5.1 Statistical Issues and Collective Evidence 35
5.2 Conclusions and Recommendations 35
Appendix 38
A.1 Supplementary Tables 38
A.2 Supplementary Figures 44
Signatures/Distribution List 48

Table of Tables

Table 1: Summary of Design Characteristics for Randomized Phase 3 Trials 8
Table 2: Summary of Treatment Distribution in the ITT Population by Trial 14
Table 3: Treatment Distribution in Safety Population, FAS Population, and Placebo-Controlled Subset of Safety Population 15
Table 4: Baseline Demographics by Treatment Group (Safety Population) 15
Table 5: Baseline CV Risk Factors and Complications by Treatment Group (Safety Population) 17
Table 6: Baseline Framingham Risk by Study and Treatment Group (Safety Population) 18
Table 7: Premature Discontinuation of Study Medication by Study and Treatment Group (FAS Population) 20
Table 8: Summary of Events of Primary Composite Endpoint by Study and Treatment Group (Safety Population) 21
Table 9: Meta-analysis Results of Primary Composite Endpoint (Safety Population)..... 22
Table 10: Sensitivity Meta-Analysis Results of Primary Composite Endpoint (Safety Population Excluding Study 1218.20) 23
Table 11: Summary of Events of Primary Composite Endpoint by Study and Treatment Group (Placebo-Controlled Subset of Safety Population) 23
Table 12: Sensitivity Meta-analysis Results of Primary Composite Endpoint (Placebo-Controlled Subset of Safety Population)..... 24
Table 13: Summary of Events of MACE by Study and Treatment Group (Safety Population) 29
Table 14: Meta-Analysis Results of Secondary Endpoints (Safety Population) 30
Table 15: Summary of Events of Primary Composite Safety Endpoint by Gender, Study and Treatment Group (Safety Population) 38
Table 16: Summary of Events of Primary Composite Safety Endpoint by Race, Study and Treatment Group (Safety Population)..... 39
Table 17: Summary of Events of Primary composite endpoint by Age Categories, Study and Treatment Group (Safety Population) 40
Table 18: Summary of Events of Primary composite endpoint by Ethnicity, Study and Treatment Group (Safety Population)..... 41
Table 19: Summary of Events of Primary composite endpoint by Baseline BMI, Study and Treatment Group (Safety Population) 42
Table 20: Summary of Events of Primary composite endpoint by Baseline Renal Impairment Status, Study and Treatment Group (Safety Population) 43

Table of Figures

Figure 1: Percentage of Subjects with Premature Discontinuation of Study Medication by Study and Treatment Group (FAS Population) 19
Figure 2: Forest Plot of Reviewer's Analysis Results of Primary Composite Endpoint (Risk difference) 25
Figure 3: Time to Event Analysis of the Primary Composite Endpoint (Safety Population, Double-Blind Treatment Phase) 26
Figure 4: Time to Event Analysis of the Primary composite endpoint Excluding Study 1218.20 (Safety Population, Double-Blind Treatment Phase)..... 27
Figure 5: Time to Event Analysis of the Primary composite endpoint (Placebo-Controlled Trials, Safety Population, Double-Blind Placebo-Controlled Phase)..... 28
Figure 6: Forest Plot of Reviewer's Analysis Results of Secondary Endpoints (M-H Risk difference)..... 31
Figure 7: Forest Plot of Reviewer's Analysis Results of Subgroups (M-H Risk Difference) 35
Figure 8: Forest Plot of Reviewer's Analysis Results of Primary composite endpoint (M-H Relative Risk)..... 44
Figure 9: Forest Plot of Reviewer's Analysis Results of Primary composite endpoint (Exact Odds Ratio)..... 45
Figure 10: Forest Plot of Reviewer's Analysis Results of Secondary Endpoints (M-H Relative Risk)..... 46
Figure 11: Forest Plot of Reviewer's Analysis Results of Subgroups (M-H Relative Risk) 47

1 Executive Summary

This statistical review and evaluation was performed in response to a consultation from the Division of Biometrics 2 (DB2) for New Drug Application (NDA) 201-280/000 (received August 9, 2010) for linagliptin tablets. The proposed indication for linagliptin is the treatment of patients with type 2 diabetes mellitus. This statistical review assesses cardiovascular (CV) related safety endpoints in the randomized phase 3 clinical development program of linagliptin (Studies 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, and 1218.50). A separate efficacy evaluation is also being reviewed by Dr. Wei Liu from DB2. This review focuses solely on safety evaluation.

1.1 Conclusions and Recommendations

Among the 8 randomized phase 3 trials for linagliptin, the trial design characteristics of Study 1218.20 differed from the other 7 trials (the only glimepiride-controlled trial, the only non-inferiority trial, and had the longest duration), and the study population in Study 1218.20 appeared to have higher baseline CV risk than all other trials. Therefore, utilizing data from Study 1218.20 and its contribution to a meta-analysis may be problematic. Due to the fact that Study 1218.20 was the only glimepiride-controlled trial, extra caution is needed when interpreting the results of the comparison between the linagliptin group and the pooled all comparator group.

Based on the meta-analysis of all 8 randomized phase 3 trials, the incidence of CV related events measured utilizing an agreed upon primary composite CV safety endpoint (composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization due to unstable angina) was found to be statistically significantly lower in the linagliptin group than in the pooled all comparator group (glimepiride, voglibose, or placebo) at the nominal α=0.05 level. The M-H risk difference between linagliptin and all comparator was -0.69% with a 95% confidence interval of (-1.17%, -0.21%). However, the results of the meta-analysis were heavily driven by Study 1218.20. One sensitivity analysis showed that, without Study 1218.20, the incidence of the primary composite endpoint was higher in the linagliptin group than in the all comparator group (voglibose or placebo) but the difference was not statistically significant. The M-H risk difference between linagliptin and all comparator was 0.06% with a 95% CI of (-0.34%, 0.46%). Furthermore, based on the placebo-controlled subset of the trials, another sensitivity analysis found no statistically significant difference between linagliptin and placebo in the incidence of primary composite endpoint. The M-H risk difference between linagliptin and placebo was -0.04% with a 95% CI of (-0.45%, 0.37%).

In Study 1218.20 also, as compared to glimepiride, linagliptin was shown to be associated with statistically significantly lower risk in developing a CV related event as measured by the primary composite endpoint. The majority of events observed in the phase 3 program for linagliptin were from Study 1218.20 and this in turn impacted the meta-analysis of the 8 trials comparing linagliptin to all comparators. Therefore, no definite conclusion can be reached on the CV safety of linagliptin in relation to a placebo or alternative active control other than glimepiride.

1.2 Brief Overview of Clinical Studies

In this NDA application, the applicant submitted 8 randomized phase 3 trials, Study 1218.15, Study 1218.16, Study 1218.17, Study 1218.18, Study 1218.20, Study 1218.23, Study 1218.35, and Study 1218.50, in support of the safety and efficacy of linagliptin for the treatment of type 2 diabetes mellitus.

All 8 randomized phase 3 trials were conducted in subjects with type 2 diabetes mellitus. Studies 1218.15, 1218.16, 1218.17, and 1218.18 were all multicenter, randomized, double-blinded, placebo-controlled, pivotal trials to compare the safety and efficacy of linagliptin and placebo for 24 weeks of treatment. Study 1218.20 was a multicenter, randomized, double-blinded, active-controlled, non-inferiority trial to compare the safety and efficacy of linagliptin and glimepiride for 104 weeks of treatment. Study 1218.23 was a multicenter, randomized, double-blinded, placebo-/active- controlled trial to compare the safety and efficacy of linagliptin and placebo for 12 weeks of treatment, and to compare the safety and efficacy of linagliptin and voglibose for 26 weeks of treatment. Study 1218.35 was a multicenter, randomized, double-blinded, placebo-controlled trial to compare the safety and efficacy of linagliptin and placebo for 18 weeks of treatment. Study 1218.50 was a multicenter, randomized, double-blinded, placebo-controlled trial to compare the safety and efficacy of linagliptin and placebo for 18 weeks of treatment (with a 34 week extension period).

In the pooled data base of the 8 randomized phase 3 trials, a total of 3,322 subjects were randomized to receive linagliptin, while a total of 979 subjects were randomized to receive placebo, and a total of 943 subjects were randomized to receive active comparator (781 to glimepiride and 162 to voglibose). Details of the 8 randomized phase 3 trials are provided in Section 3.1.1.

1.3 Statistical Issues and Findings

The primary agreed upon safety endpoint was a composite endpoint made up by CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization due to unstable angina.

Phase 3 data from the 8 randomized studies were pooled to evaluate the risk of developing a CV related event as measured by the primary composite endpoint. In this review, the comparison of incidence between the linagliptin group and the pooled all comparator group (including comparators of glimepiride, voglibose, or placebo) was performed using the Mantel-Haenszel (M-H) risk difference approach with study as stratification factor. The M-H relative risk ratio approach and the exact stratified odds ratio approach were also applied to evaluate the relative risk ratio or odds ratio of linagliptin. Stratified log-rank test and stratified Cox proportional hazards regression model were performed for the time-to-event analyses. More details for the statistical methodologies used in this review are provided in Section 3.1.2.

Based on the pooled data of all 8 randomized phase 3 trials, a total of 34 events of the primary composite endpoint were reported, 11 occurred in the linagliptin group and 23 occurred in the pooled all comparator group. The incidence of the primary composite endpoint was 0.33% (11/3319) in the linagliptin group, as compared to 1.20% (23/1920) in the all comparator group. The M-H risk difference between linagliptin and all comparator was -0.69% with a 95% confidence interval (CI) of (-1.17%, -0.21%). The M-H relative risk ratio between linagliptin and all comparator was 0.34 with a 95% CI of (0.15, 0.74), and similar results were seen for the exact stratified odds ratio. Detailed analysis results are provided in Section 3.1.6.1.1 and Section 3.1.6.1.4.

The meta-analysis results for the primary composite endpoint were heavily driven by Study 1218.20. Because Study 1218.20 had different trial design characteristics than the other 7 trials (the only glimepiride-controlled trial, the only non-inferiority trial, and had the longest duration), and the study population in Study 1218.20 appeared to have higher baseline CV risk than all other trials, the heavy impact of Study 1218.20 on the overall meta-analysis results is of concern. Among the total of 23 events of the primary composite endpoint reported in the pooled all comparator group, 20 occurred in the glimepiride arm in Study 1218.20. Therefore, two sensitivity analyses were performed to assess the robustness of the meta-analysis results. Without Study 1218.20, the incidence of the primary composite endpoint was 0.31% (8/2541) in the linagliptin group, as compared to 0.26% (3/1139) in the all comparator group. The M-H risk difference between linagliptin and all comparator was 0.06% with a 95% CI of (-0.34%, 0.46%), and the M-H relative risk ratio of linagliptin was 1.21 with a 95% CI of (0.35, 4.26). Furthermore, direct comparison between linagliptin and placebo was evaluated based on the placebo-controlled subset of the randomized phase 3 trials. The incidence rate of primary composite endpoint was 0.24% (6/2541) in the linagliptin group, as compared to 0.31% (3/977) in the placebo group. The M-H risk difference between linagliptin and placebo was -0.04% with a 95% CI of (-0.45%, 0.37%), and the M-H relative risk ratio of linagliptin was 0.86 with a 95% CI of (0.23, 3.26). Detailed sensitivity analysis results are provided in Section 3.1.6.1.2 and Section 3.1.6.2.4.

Several secondary endpoints were also evaluated in this review, including custom major adverse cardiovascular event (MACE) and each component of the primary composite endpoint. The results for MACE or non-fatal stroke were both close to the results for the primary composite endpoint. Results for other secondary endpoints (CV death, non-fatal MI, and hospitalization due to unstable angina) were in the same direction as the primary composite endpoint, but did not reach statistical significance. Detailed analysis results for the secondary endpoints are provided in Section 3.1.6.2.

The difference between linagliptin and all comparator in developing a CV related event as measured by the primary composite endpoint were also evaluated in several subgroups. Most of the subgroup analysis results were in the same direction as the overall result for the primary composite endpoint. Detailed results for subgroup analyses are provided in Section 4.

2 Introduction

2.1 Product Description

Linagliptin is a selective, orally administered, xanthine-based Dipeptidyl-dipeptidase-4 (DPP-4) inhibitor. The proposed indication of linagliptin is to improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise. The proposed therapeutic dose of linagliptin is 5 mg.

2.2 Clinical Trial Overview

The applicant submitted the results of 4 large phase 3 pivotal, double-blind, placebo-controlled trials (Studies 1218.15, 1218.16, 1218.17, and 1218.18) with duration of treatment of 24 weeks in support of the safety and efficacy of Linagliptin for treatment of type 2 diabetes mellitus. The applicant also provided 4 additional phase 3 trials for further evidence: a double-blind active-controlled trial that provides long-term efficacy data (Study 1218.20), 2 studies with double-blind placebo-controlled treatment periods of 18 weeks duration (Studies 1218.35 and 1218.50), and a placebo- and active-controlled study with an extension period which provides efficacy data over 52 weeks (Study 1218.23). The summary of design characteristics of these 8 trials is presented in Table 1.

Reviewer's comment: *Another submitted phase 3 trial (Study 1218.40) was an open-label extension trial of the four pivotal trials (Studies 1218.15, 1218.16, 1218.17 and 1218.18), therefore was not evaluated in this review. The meta-analyses in this review are focused on the 8 randomized phase 3 trials.*

Table 1: Summary of Design Characteristics for Randomized Phase 3 Trials

Study Name	Treatment Arms	Study Size	Duration	Comparison
1218.15	linagliptin, placebo	389	24 weeks	Superiority
1218.16	linagliptin, placebo	503	24 weeks	Superiority
1218.17	linagliptin, placebo	701	24 weeks	Superiority
1218.18	linagliptin, placebo	1058	24 weeks	Superiority
1218.20	linagliptin, ***glimepiride***	1560	104 weeks	Non-inferiority
1218.23	linagliptin, placebo, ***voglibose***	561	26 weeks *	Superiority
1218.35	linagliptin, placebo	245	18 weeks	Superiority
1218.50	linagliptin, placebo	227	18 weeks**	Superiority

* With a 26 week extension period after the 26 week double-blinded phase
** With a 34 week active-controlled extension period after the 18 week placebo-controlled phase
Source: Created by reviewer.

2.3 Data Sources

The applicant submitted electronic documents and datasets for Studies 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35 and 1218.50. The following files available within the CDER Electronic Document Room (EDR) were utilized in this review.

\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0015
\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0016
\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0017
\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0018
\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0020ia
\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0023
\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0035
\\Cdsesub1\evsprod\NDA201280\0000\m5\datasets\1218-0050ia
\\Cdsesub1\evsprod\NDA201280\0017\m5\datasets\u10-1736\analysis

3 Statistical Evaluation

This review is focused on the meta-analysis of cardiovascular (CV) risk. For a complete statistical evaluation of efficacy results, please refer to the review authored by Dr. Wei Liu.

3.1 Evaluation of Safety

The review of CV safety comprises data from Studies 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, and 1218.50. Based upon interactions with the clinical review team, the following review of safety consists of a focused evaluation of CV endpoints. All comparative analyses are between the randomized treatment groups, linagliptin and comparator, or linagliptin and placebo.

3.1.1 Study Designs

Study 1218.15 was a phase 3 multicenter, randomized, double-blinded, placebo-controlled study. Study 1218.15 was conducted at 43 sites in 7 countries outside the United States, in male and female subjects between 18 and 80 years of ago with type 2 diabetes with insufficient glycaemic control. A total of 389 subjects were randomized in a 2:1 fashion to linagliptin plus pioglitazone or placebo plus pioglitazone. Randomization was stratified by HbA_{1c} value at the beginning of the placebo run-in period (< 8.5% or ≥ 8.5%) and the prior use of anti-diabetic drugs (none, monotherapy, combination therapy). Study 1218.15 was powered to provide 97% or greater power to detect a mean difference of 0.7% between linagliptin and placebo in HbA_{1c} change from baseline to week 24.

Study 1218.16 was a phase 3 multicenter, randomized, double-blinded, placebo-controlled study. Study 1218.16 was conducted at 66 sites in 11 countries outside the United States, in male and female subjects between 18 and 80 years of ago with type 2 diabetes with insufficient glycaemic control (either drug naïve or despite with one oral anti-diabetic agent). A total of 503 subjects were randomized in a 2:1 fashion to linagliptin or placebo. Randomization was stratified by HbA_{1c} value at the beginning of the placebo run-in period (< 8.5% or ≥ 8.5%) and the prior use of anti-diabetic drugs (none or monotherapy). Study 1218.16 was powered to provide 95% or greater power to

detect a mean difference of 0.7% between linagliptin and placebo in HbA_{1c} change from baseline to week 24.

Study 1218.17 was a phase 3 multicenter, randomized, double-blinded, placebo-controlled study. Study 1218.17 was conducted at 82 sites in 10 countries including the United States, in male and female subjects between 18 and 80 years of ago with type 2 diabetes with insufficient glycaemic control despite therapy with metformin. A total of 701 subjects were randomized in a 3:1 fashion to linagliptin or placebo in addition to ongoing background metformin therapy. Randomization was stratified by HbA_{1c} value at the beginning of the placebo run-in period (< 8.5% or ≥ 8.5%) and the prior use of anti-diabetic drugs (metformin monotherapy or combination therapy). Study 1218.17 was powered to provide 95% or greater power to detect a mean difference of 0.7% between linagliptin and placebo in HbA_{1c} change from baseline to week 24.

Study 1218.18 was a Phase 3 multicenter, randomized, double-blinded, placebo-controlled study. Study 1218.18 was conducted at 100 sites in 11 countries outside the United States, in male and female subjects between 18 and 80 years of age with type 2 diabetes with insufficient glycaemic control despite therapy with combination of metformin and sulphonylurea. A total of 1058 subjects were randomized in a 3:1 fashion to linagliptin or placebo. Randomization was stratified by the HbA_{1c} value at the beginning of the placebo run-in period (<8.5% or ≥8.5%). Study 1218.18 was powered to provide 99% or greater power to detect a mean difference of 0.7% between linagliptin and placebo in HbA_{1c} change from baseline to week 24.

Study 1218.23 was a Phase 3 multicenter, randomized, double-blinded, placebo-controlled/active-controlled study. Study 1218.23 was conducted at 48 sites in Japan, in male and female Japanese subjects between 20 and 80 years of age with type 2 diabetes with insufficient glycaemic control despite being treated with diet and/or exercise only or with oral anti-diabetic drugs. A total of 561 subjects were randomized in a 1:2:2:2 fashion to one of the following four treatment groups: placebo, linagliptin 5 mg, linagliptin 10 mg, and voglibose (two linagliptin does groups were combined in the meta-analysis). A dynamic allocation method was used to achieve homogeneity in the following three allocation factors across the four treatment groups: HbA1c value at the beginning of the placebo run-in period (<8.5% or ≥8.5%), number of previously used anti-diabetic drugs (0, 1, or 2), and gender (male or female). Study 1218.23 was powered to provide 90% or greater power to detect a mean difference of 0.5% between linagliptin and placebo in HbA1c change from baseline to week 12, and 90% or greater power to detect a mean difference of 0.45% between linagliptin and voglibose in HbA1c change from baseline to week 26.

Study 1218.35 was a Phase 3 multicenter, randomized, double-blinded, placebo-controlled study. Study 1218.35 was conducted at 45 sites in 7 countries including the United States, in male and female subjects between 18 and 80 years of age with type 2 diabetes with insufficient glycaemic control despite therapy with a sulfonylurea drug. A total of 245 subjects were randomized in a 2:1 fashion to linagliptin or placebo. Randomization was stratified by the HbA_{1c} value at the beginning of the placebo run-in

period (<8.5% or ≥8.5%) and the prior use of anti-diabetic drugs (sulfonylurea monotherapy or combination therapy). Study 1218.35 was powered to provide 90% or greater power to detect a mean difference of 0.7% between linagliptin and placebo in HbA_{1c} change from baseline to week 18.

Study 1218.50 was a Phase 3 multicenter, randomized, double-blinded, placebo-controlled/active-controlled study. Study 1218.50 was conducted at 53 sites in 7 countries including the United States, in male and female subjects between 18 and 80 years of age with type 2 diabetes with insufficient glycaemic control for whom metformin therapy was inappropriate (intolerability or contraindication). A total of 227 subjects were randomized in a 2:1 fashion to linagliptin or placebo. Randomization was stratified by the HbA_{1c} value at the beginning of the placebo run-in period (<8.5% or ≥8.5%), the prior use of anti-diabetic drugs (none or monotherapy), and reason for ineligibility for treatment with metformin (gastrointestinal side effects or high creatinine levels). Study 1218.50 was powered to provide 97% or greater power to detect a mean difference of 0.7% between linagliptin and placebo in HbA_{1c} change from baseline to week 18. After the 18 week placebo-controlled phase, Study 1218.50 had a 34 week active-controlled extension period (subjects previously treated with placebo switch to glimerpiride in a blinded fashion). Only the placebo-controlled phase based on the pre-specified 18 weeks interim analysis was included in the meta-analysis.

Unlike the other 7 randomized phase 3 superiority trials, Study 1218.20 was a Phase 3 multicenter, randomized, double-blinded, active-controlled non-inferiority trial. Study 1218.20 was conducted at 209 sites in 16 countries including the United States, in male and female subjects between 18 and 80 years of age with type 2 diabetes previously treated with metformin monotherapy or metformin plus not more than 1 other oral anti-diabetic agent (unchanged for 10 weeks). A total of 1560 subjects were randomized in a 1:1 fashion to linagliptin or glimepiride. Randomization was stratified by the HbA1c value at the beginning of the placebo run-in period (<8.5% or ≥8.5%), and the prior use of anti-diabetic drugs (monotherapy or combination therapy). Study 1218.20 was powered to provide 90% or greater power to demonstrate the non-inferiority of linagliptin compared to glimepiride with a non-inferiority margin of 0.35% in HbA1c change from baseline to week 104. Only results based on the pre-specified 52 week interim analysis were included in the meta-analysis.

3.1.2 Statistical Methodologies

In the following sections, statistical methods and tabulations are presented for the evaluation of safety only.

3.1.2.1 Methods of Imputing Missing

As specified in the protocol, subjects who did not experience a specific event of interest were right-censored at the last day of treatment intake + 7 days.

3.1.2.2 Analysis of Event Incidence

The applicant proposed to analyze the occurrence of CV related events as a binary endpoint using the stratified exact test for the common odds ratio and by Cochran-Mantel-Haenszel (CMH) test for the relative risk.

Reviewer's comment: *Both the exact stratified odds ratio and the CMH relative risk approaches are acceptable to compare the incidence of primary composite endpoint between linagliptin and control, but both approaches can not handle trials with zero events. More details are provided in Section 3.1.2.4.*

In this review, the primary analysis method was Mantel-Haenszel risk difference and the associated 95% confidence interval. This method makes use of all trials including trials with no events of interest. The unit of analysis was the subject and the stratification factor was the trial. For trials with more than two arms, arms that were part of the same comparison group (linagliptin versus comparator) were combined. Confidence intervals of risk difference for individual trials were based on exact method.

Other than risk difference, it is also of clinical importance to assess the relative risk ratio between linagliptin and comparator. Mantel-Haenszel method was applied to estimate the relative risk ratio and the associated 95% confidence interval. Similarly, the unit of analysis was the subject and the stratification factor was the trial. Confidence intervals of the relative risk ratio for individual trials were based on exact method.

For the primary composite endpoint, an additional exact method for stratified odds ratio and associated 95% confidence interval was applied. The stratification factor was also the trial. Confidence intervals of odds ratio for individual trials were based on exact method.

3.1.2.3 Time-to-Event Analysis

The applicant proposed to use Cox proportional hazards regression model and Poisson regression model for the time-to-event analyses.

Reviewer's comment: *For time-to-event analysis, the stratified log-rank test and the stratified Cox regression model are preferred as they require fewer assumptions and are more robust than the Cox regression and Poisson model used by the applicant.*

In this review, for the time-to-event analysis of the primary composite endpoint, the stratified log-rank test was applied to compare the linagliptin group and the control group, and the stratified Cox proportional hazards regression model was applied to test the hazard ratio of linagliptin versus control.

3.1.2.4 Handling of Trials with zero events

According to the applicant, two different forms of continuity correction were applied for the CMH test to deal with trials with zero events. For statistical methods other than CMH test, trials of identical treatment allocations were pooled until achieving at least one event in each treatment group. If this was not sufficient, trials of similar allocation ratios were pooled until at least one event in the linagliptin and the control group was observed. Instead of the studies as such, these pools of studies were used as a stratification factor in the analysis.

Reviewer's comment: *Continuity corrections, especially the 0.5 correction, are somewhat arbitrary and problematic because they might bring not only additional bias but also inflation of Type 1 error rate.*

Reviewer's comment: *The applicant proposed to pool studies with identical treatment allocation ratio to deal with trials with zero events. This is not a commonly accepted approach to deal with meta-analysis of rare event since the stratification factor is no longer preserved in the study. In practice, the applicant not only pooled studies with identical treatment allocation ratio, but also studies with 'similar' allocation ratio. This might be even more problematic, since pooling studies with different allocation ratio might bring additional bias to the result.*

Among the analysis methods used in this review, the primary analysis method (M-H risk difference) does not require special handling of trials with zero events. For the sensitivity analysis methods (M-H relative risk, stratified odds ratio, and stratified Cox regression), trials with zero events were excluded from the analysis.

3.1.3 Populations

As shown in Table 2, among the 5,244 randomized subjects in the Intern-to-Treat (ITT) population from the 8 randomized phase 3 trials, 3,322 (63.3%) subjects were randomized to receive linagliptin, while 979 (18.7%) subjects were randomized to receive placebo, and 943 (18.0%) subjects were randomized to receive active comparator drugs (781 (14.9%) to glimepiride and 162 (3.1%) to voglibose).

Table 2: Summary of Treatment Distribution in the ITT Population by Trial

Study	Number of Subjects, N (%)			
	All Linagliptin	Placebo	Active Comparator	Combined Comparator
1218.15 (N=389)	259 (66.6)	130 (33.4)	-	130 (33.4)
1218.16 (N=503)	336 (66.8)	167 (33.2)	-	167 (33.2)
1218.17 (N=701)	524 (74.8)	177 (25.2)	-	177 (25.2)
1218.18 (N=1058)	793 (75.0)	265 (25.0)	-	265 (25.0)
1218.20 (N=1560)	779 (49.9)	-	781 (50.1)	781 (50.1)
1218.23 (N=561)	319 (56.9)	80 (14.3)	162 (28.9)	242 (43.1)
1218.35 (N=245)	161 (65.7)	84 (34.3)	-	84 (34.3)
1218.50 (N=227)	151 (66.5)	76 (33.5)	-	76 (33.5
Total (N=5244)	3322 (63.3)	979 (18.7)	943 (18.0)	1922 (36.7)

Source: Created by reviewer.

The applicant's efficacy analyses were focused on a modified intent-to-treat population: the full analysis set (FAS) population, which included all randomized patients who received at least one dose of study medication, had a baseline HbA_{1c} measurement, and had at least one on-treatment HbA_{1c} measurement. HbA_{1c} measurements were regarded as 'on-treatment' if they were taken after the first dose of study medication and up to 7 days after the last dose of study medication had been administered. In this review, all the analyses for CV outcome are primarily based on the safety population. The safety population included all randomized subjects who received at least one dose of randomized study treatment. In order to assess the direct comparison between linagliptin and placebo, it is also of clinical interest to conduct sensitivity analysis in the placebo-controlled subset of the safety population. The placebo-controlled subset of the safety population included all the subjects in the safety population that were randomized to linagliptin or placebo. Furthermore, studies with treatment switch after the end of placebo-controlled phase (Study 1218.23 and Study 1218.50) were censored at the end of the placebo-controlled phase.

As shown in Table 3, among the 5,244 randomized subjects in the ITT population, a total of 5,239 (99.9%) subjects were included in the safety population, while 5,152 (98.2%) subjects were included in the FAS population, and 3,518 (67.1%) subjects were included in the placebo-controlled subset of safety population.

Table 3: Treatment Distribution in Safety Population, FAS Population, and Placebo-Controlled Subset of Safety Population

	All Linagliptin	Placebo	Active Comparator	Combined Comparator
Total Number of Subjects (ITT Population)	3322	979	943	1922
Safety Population	3319 (99.9)	977 (99.8)	943 (100.0)	1920 (99.9)
FAS Population	3266 (98.3)	963 (98.4)	923 (97.9)	1886 (98.1)
Placebo-Controlled Subset of Safety Population	2541(76.5)	977 (99.8)	0 (0.0)	977 (50.8)

Source: Created by reviewer.

3.1.4 Subject Disposition, Demographic and Baseline Characteristics

As shown in Table 4, in the safety population, baseline demographics were similar among the treatment groups. In the safety population, there were slightly more male subjects than female subjects (55% versus 45%). Approximately 60% of subjects were White and about 38% were Asian, while less than 2% of subjects were Black or African American. Furthermore, about 10% subjects in the safety population were with Hispanic or Latino ethnicity. More than 78% of subjects in the safety population were above 50 years of age, while the mean age was about 58. More than 38% of subjects had body mass index (BMI) greater than 30 kg/m^2, while the mean BMI was about 29 kg/m^2.

Table 4: Baseline Demographics by Treatment Group (Safety Population)

	Linagliptin	Placebo	Active Comparator	Total Comparator
N treated (% female)	3319 (46.3%)	977 (45.3%)	943 (37.2%)	1920 (41.4%)
Age (years) ≤ 50 years 50 – 65 years ≥ 65 years	58±10 21.6% 50.4% 28.0%	57±10 25.8% 49.6% 24.6%	60±10 17.8% 49.4% 32.8%	58±10 21.9% 49.5% 28.6%
BMI (kg/m^2) 25 – 30 ≥ 30	28.8±5.0 38.0% 37.8%	28.7±5.0 38.5% 36.1%	29.5±4.8 36.5% 45.4%	29.1±4.9 37.5% 40.7%
Race and ethnicity				
White Black Asian	59.7% 1.4% 38.9%	54.0% 1.3% 44.6%	69.9% 1.9% 28.2%	61.8% 1.6% 36.6%
Not hispanic/Latino Hispanic/Latino Missing	88.0% 11.8% 0.2%	85.8% 13.6% 0.6%	97.9% 2.0% 0.1%	91.7% 7.9% 0.4%

Source: Applicant's Clinical Trial Report (Metaanalysis Report), Page 23, Table 4.

Baseline CV risk factors and complications are presented in Table 5. In the safety population, approximately 11% of subjects had previously diagnosed coronary artery disease (CAD), while about 3% had cerebrovascular disease (CVD) or peripheral artery disease (POAD), respectively. Furthermore, more than 64% of subjects were hypertensive and more than 38% were current or ex- smoker. According to the 4-variable modification of diet in renal diseases (MDRD) formula for estimation of glomerular filtration rate (GFR), more than 44% of subjects had some degree of renal impairment.

As shown in Table 5, the pooled estimated CV risk based on the Framingham score was higher in the active comparator group, as compared to the linagliptin group or the placebo group (mean Framingham risk of 11.6% versus 9.8% or 9.1%). Approximately 38% of subjects in the active comparator group had Framingham risk >15%, compared to 28% in the linagliptin group and 25% in the placebo group. Similarly, the prevalence of previous CAD, CVD, POAD, or hypertension was higher in the active comparator group than in the linagliptin group or the placebo group.

Table 5: Baseline CV Risk Factors and Complications by Treatment Group (Safety Population)

	Linagliptin	Placebo	Active Comparator	Total Comparator
n	3319	977	943	1920
Metabolic syndrome	60.3%	55.9%	67.8%	61.7%
Previous CAD	10.4%	10.1%	11.9%	11.0%
Previous CVD	2.9%	3.6%	4.1%	3.9%
Previous POAD	2.3%	2.7%	3.3%	3.0%
Hypertension	63.8%	60.2%	72.1%	66.0%
Never smoked	62.7%	64.8%	54.8%	59.9%
Ex-smoker	22.9%	19.1%	29.5%	24.2%
Current smoker	14.4%	16.1%	15.7%	15.9%
Renal function as determined by estimated GFR using Cockroft-Gault/MDRD formula				
Normal	74.9%/55.4%	76.7%/58.3%	78.0%/52.3%	77.3%/55.4%
Mildly impaired	19.9%/37.3%	18.3%/34.9%	18.7%/41.4%	18.5%/38.1%
Moderately impaired	2.2%/4.3%	2.7%/4.5%	4.1%/4.1%	1.9%/4.3%
Severely impaired	0.1%/0.1%	0.2%/0.1%	0%/0%	0.1%/0.1%
Missing	2.9%/2.9%	2.1%/2.1%	2.2%/2.2%	2.2%/2.2%
ASA	29.5%	28.8%	32.2%	30.5%
Any anti-HT drug	60.0%	56.4%	69.8%	63.0%
Beta-blockers	32.7%	31.8%	34.3%	33.2%
ACE inhib	44.8%	45.6%	34.3%	43.5%
ARBs	22.0%	21.8%	21.0%	21.9%
Diuretics	22.9%	23.3%	41.3%	22.0%
Others	46.9%	64.0%	77.7%	49.6%
Any lipid lowering therapy	39.5%	36.5%	47.9%	42.1%
Statins	86.6%	84.3%	92.5%	88.9%
Fibrates	14.9%	19.7%	7.3%	12.7%
Others	8.3%	7.3%	8.5%	8.2%
Any ASA, anti-HT or lipid lowering therapy	72.8%	69.7%	81.5%	75.5%
Estimated 10 year risk for coronary heart disease based on Framingham score				
Framingham risk	9.8±8.2%	9.1±8.1%	11.6±8.6%	10.3±8.4%
Framingham risk > 15%	27.8%	24.7%	37.8%	31.1%

Abbreviations: CAD – coronary artery disease, CVD – cerebrovascular disease, POAD – peripheral artery disease, ASA - Acetyl salicylic acid, HT – hypertensive, ACE – angiotensinogen converting enzyme, ARB – angiotensin II receptor blocker

Source: Applicant's Clinical Trial Report (Metaanalysis Report), Page 26, Table 6.

Within each of the 8 randomized phase 3 studies, the baseline CV risk factors were well balanced between linagliptin and comparator. For example, the baseline Framingham risk scores are presented in Table 6. For each study, the scores were similar between the linagliptin group and the placebo group, or between linagliptin and active comparator, depending on the study design. On the other hand, the pooled Framingham risk scores at baseline were quite different among the 8 randomized phase 3 trials (Table 6). Subjects from the two trials involving active comparator (Study 1218.20 and Study 1218.23, especially Study 12180.20) had higher Framingham risk scores, compared to subjects from the other 6 placebo-controlled trials. The overall mean Framingham risk score was 11.66% in Study 1218.20 and 11.17% in Study 1218.23, while the score ranged from 8.20% to 10.40% among the 6 placebo-controlled phase 3 trials.

Reviewer's comment: *The observed differences in CV risk factors among the* ***pooled*** *linagliptin group, the* ***pooled*** *placebo group, and the* ***pooled*** *active comparator group (Table 5) were not due to the imbalance between randomized groups within any of the 8 trials. Instead, the differences among the studies might be the potential cause. Subjects in the active-controlled trial Study 1218.20 appeared to have higher CV risk than subjects from other placebo-controlled trials. This should be of concern when conducting meta-analysis based on Study 1218.20 and other placebo-controlled trials.*

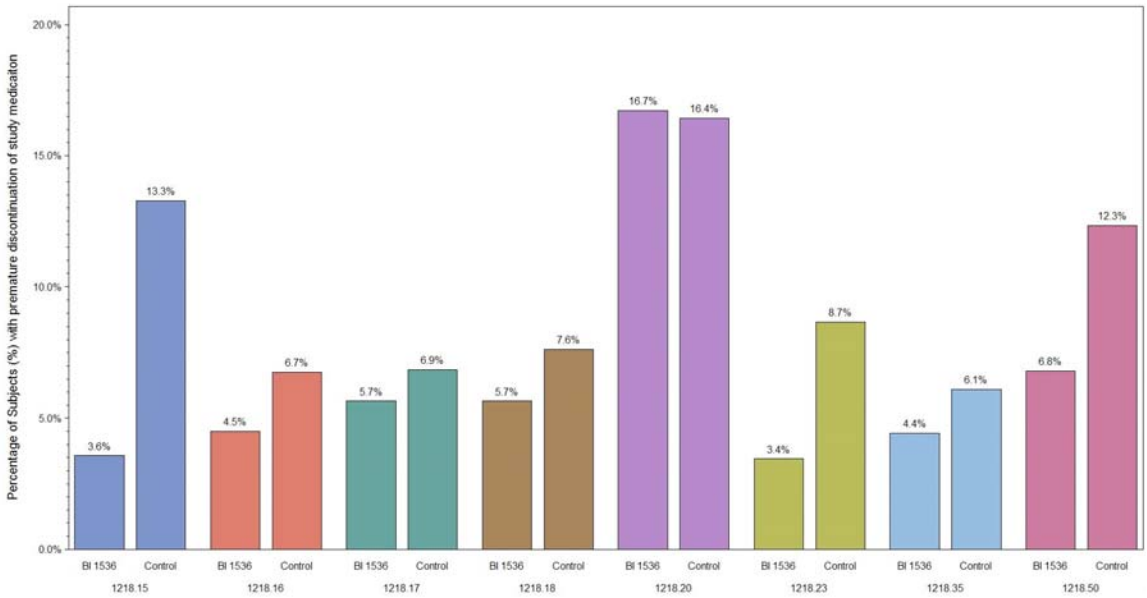
Table 6: Baseline Framingham Risk by Study and Treatment Group (Safety Population)

Study	Mean risk score (%) (Percentage of subjects with risk score >15%)			
	All Linagliptin	Placebo	Active Comparator	Total
1218.15	10.07 (29.0)	11.07 (36.2)	-	10.40 (31.4)
1218.16	8.63 (23.8)	7.47 (16.8)	-	8.24 (21.5)
1218.17	8.57 (22.0)	8.87 (25.4)	-	8.65 (22.9)
1218.18	9.24 (26.5)	8.67 (20.9)	-	9.10 (25.1)
1218.20	11.65 (35.9)	-	11.67 (37.9)	11.66 (36.9)
1218.23	11.09 (32.6)	11.18 (33.8)	11.32 (37.0)	11.17 (34.0)
1218.35	8.66 (21.1)	9.36 (25.0)	-	8.90 (22.4)
1218.50	7.94 (17.2)	8.72 (23.7)	-	8.20 (19.4)

Source: Created by reviewer.

Among the 5,152 subjects in the FAS population from the 8 randomized phase 3 trials, approximately 9% of them (473/5152) prematurely discontinued study medication. As presented in Figure 1, the percentage of subjects with premature discontinuation of study medication tended to be lower in the linagliptin treatment groups than in the comparator groups. On average, 7.8% of the subjects in the linagliptin group discontinued study medication, which was statistically significantly lower than the comparator group (11.7%) with p-value=0.008 (CMH test stratified by studies).

Figure 1: Percentage of Subjects with Premature Discontinuation of Study Medication by Study and Treatment Group (FAS Population)



* In Study 1218.23, the Control group included both the placebo group and the voglibose group
Source: Created by reviewer.

As presented in Table 7, the most common reasons reported for study medication discontinuation were adverse event, and administrative reasons, which accounted for 3.5% and 3.3% of subjects in the FAS population respectively. On average, 2.5% of the subjects in the linagliptin group discontinued study medication due to adverse events, which was statistically significantly lower than the comparator group (5.3%) with p-value=0.0007 (CMH test stratified by studies). Similarly, 2.9% of the subjects in the linagliptin group discontinued study medication for administrative reason (based on applicant's definition, this included non compliance to protocol, lost to follow-up, and refuse to continue medication), which was partially statistically significantly lower than the comparator group (3.9%) in the comparator group with p-value=0.07 (CMH test stratified by studies).

Table 7: Premature Discontinuation of Study Medication by Study and Treatment Group (FAS Population)

Study	Arms	Sample Size	Prematurely Discontinued Study Medicine n (%)	Adverse Event n (%)	Admin Reason n (%)	Lack of Efficacy n (%)	Other n (%)
1218.15	linagliptin	252	9 (3.6)	3 (1.2)	4 (1.6)	1 (0.4)	1 (0.4)
	placebo	128	17 (13.3)	5 (3.9	8 (6.3)	1 (0.8)	3 (2.3)
1218.16	linagliptin	333	15 (4.5)	4 (1.2)	7 (2.1)	0 (0.0)	4 (1.2)
	placebo	163	11 (6.7)	3 (1.8)	2 (1.2)	2 (1.2)	4 (2.5)
1218.17	linagliptin	513	29 (5.7)	5 (1.0)	16 (3.1)	1 (0.2)	7 (1.4)
	placebo	175	12 (6.9)	3 (1.7)	7 (4.0)	0 (0.0)	2 (1.1)
1218.18	linagliptin	778	44 (5.7)	16 (2.1)	26 (3.3)	2 (0.3)	0 (0.0)
	placebo	262	20 (7.6)	4 (1.5)	12 (4.6)	4 (1.5)	0 (0.0)
1218.20	linagliptin	766	128 (16.7)	39 (5.1)	34 (4.4)	29 (3.8)	26 (3.4)
	glimepiride	761	125 (16.4)	64 (8.4)	34 (4.5)	9 (1.2)	18 (2.4)
1218.23	linagliptin	319	11 (3.4)	8 (2.5)	1 (0.3)	0 (0.0)	2 (0.6)
	placebo/ ***voglibose***	242	21 (8.7)	18 (7.4)	3 (1.2)	0 (0.0)	0 (0.0)
1218.35	linagliptin	158	7 (4.4)	5 (3.2)	1 (0.6)	0 (0.0)	1 (0.6)
	placebo	82	5 (6.1)	2 (2.4)	2 (2.4)	0 (0.0)	1 (1.2)
1218.50	linagliptin	147	10 (6.8)	1 (0.7)	6 (4.1)	2 (1.4)	1 (0.7)
	placebo	73	9 (12.3)	0 (0.0)	6 (8.2)	1 (1.4)	2 (2.7)

* In Study 1218.23, the Control group included both the placebo group and the voglibose group
Source: Created by reviewer.

3.1.5 Endpoints

3.1.5.1 Primary Composite Endpoints

The primary safety endpoint is a composite endpoint, consisting of the following events:

- CV death (including fatal stroke and fatal MI)
- non-fatal MI
- non-fatal stroke
- hospitalization due to unstable angina

The choice of the primary composite endpoint was agreed upon by the clinical team. The occurrence of the endpoint will be evaluated, resulting in the number of patients with at least one of the events above and the relative frequency with respect to the number of treated patients. The time to the first occurrence of any of the components above will be considered for all patients as well. Patients without events will be considered censored at the end of the observation period.

3.1.5.2 Secondary Endpoints

The secondary endpoints are the occurrence of each the following events:

- FDA defined custom Major Adverse Cardiovascular Event (MACE), derived from 34 MedDRA preferred terms
- Each component of the primary composite endpoint

3.1.6 Results and Conclusions

3.1.6.1 Primary Composite Endpoint

3.1.6.1.1 Analysis of Incidence

The summary of the primary composite endpoint in the safety population is presented in Table 8. Among the 5,244 subjects in the safety population, 34 subjects have an event that was counted in the primary composite endpoint. To be more specific, a total of 4, 13, 13 and 4 subjects were reported to have CV death, non-fatal MI, non-fatal stroke, and hospitalization due to unstable angina, respectively. Among the 8 trials, Study 1218.16 was the only study that had no events. On the other hand, 23 out of the 34 events occurred in Study 1218.20, while only 1 to 3 events occurred in any of the other 6 trials.

Table 8: Summary of Events of Primary Composite Endpoint by Study and Treatment Group (Safety Population)

Study	Arms	Sample Size	Primary Composite Endpoint n (%)	CV Death n (%)	Non-fatal MI n (%)	Non-fatal Stroke n (%)	UA with Hosp* n (%)
1218.15	linagliptin	259	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
	placebo	130	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.16	linagliptin	336	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	placebo	167	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.17	linagliptin	523	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
	placebo	177	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
1218.18	linagliptin	792	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
	placebo	263	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
1218.20	linagliptin	778	3 (0.4)	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)
	glimepiride	781	20 (2.6)	2 (0.3)	6 (0.8)	10 (1.3)	2 (0.3)
1218.23	linagliptin	319	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
	placebo/ ***voglibose***	242	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.35	linagliptin	161	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
	placebo	84	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.50	linagliptin	151	2 (1.3)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
	placebo	76	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

* UA with Hosp – Hospitalization due to unstable angina
Source: Created by reviewer.

In the safety population, the meta-analysis results of the primary composite endpoint based on all 8 randomized phase 3 trials are presented in Table 9. The incidence of CV related events was found to be statistically significantly lower in the linagliptin group

than in the all comparator group. The M-H risk difference between linagliptin and all comparator was -0.69% with a 95% CI of (-1.17%, -0.21%). Similarly, the M-H relative risk ratio between linagliptin and all comparator was 0.34 with a 95% CI of (0.15, 0.74), and the exact stratified odds ratio between linagliptin and all comparator was 0.36 with a 95% CI of (0.16, 0.78).

Table 9: Meta-analysis Results of Primary Composite Endpoint (Safety Population)

	Linagliptin	All Comparator
Incidence of events	11/3319 (0.33%)	23/1920 (1.20%)
M-H Risk Difference (95% CI)	-0.69% (-1.17%, -0.21%)	
M-H Relative Risk Ratio (95% CI)	0.34 (0.15, 0.74)	
Exact Stratified Odds Ratio (95% CI)	0.36 (0.16, 0.78)	

Source: Created by reviewer.

3.1.6.1.2 Sensitivity Analyses of Incidence

As discussed in Section 3.1.1, the design characteristics of Study 1218.20 differed from the other 7 trials. For example, Study 121820 was the only glimepiride-controlled trial, the only non-inferiority trial, and had the longest duration. Furthermore, Table 6 in Section 3.1.4 showed that subjects in Study 1218.20 tended to have higher CV risk than subjects in other trials. In addition, Table 8 in Section 3.1.6.1.1 showed that the majority of events were from Study 1218.20 and occurred in the glimepiride group. Therefore, it was important to consider the impact of Study 1218.20 on the meta-analysis of the primary composite endpoint based on all 8 trials, and to evaluate the robustness of the meta-analysis results shown in Table 9.

Excluding Study 1218.20

The first sensitivity analysis of the primary composite endpoint was to conduct the meta-analysis after excluding Study 1218.20. As shown in Table 8, with the exclusion of Study 1218.20, a total of 11 events occurred in the safety population of the other 7 trials, with 8 reported in the linagliptin group and 3 reported in the all comparator group. The results of the sensitivity analysis excluding Study 1218.20 are presented in Table 10. In the safety population with the exclusion of Study 1218.20, the incidence of CV related events was not statistically significantly different between the linagliptin group and the all comparator group. The M-H risk difference between linagliptin and all comparator was 0.06% with a 95% CI of (-0.34%, 0.46%). The corresponding M-H relative risk ratio between linagliptin and all comparator was 1.21 with a 95% CI of (0.35, 4.26), and the exact stratified odds ratio was 1.23 with a 95% CI of (0.29, 7.27).

Table 10: Sensitivity Meta-Analysis Results of Primary Composite Endpoint (Safety Population Excluding Study 1218.20)

	Linagliptin	All Comparator
Incidence of events	8/2541 (0.31%)	3/1139 (0.26%)
M-H Risk Difference (95% CI)	0.06% (-0.34%, 0.46%)	
M-H Relative Risk Ratio (95% CI)	1.21 (0.35, 4.26)	
Exact Stratified Odds Ratio (95% CI)	1.23 (0.29, 7.27)	

Source: Created by reviewer.

Placebo-Controlled Subset of Safety Population

A second sensitivity analysis of the primary composite endpoint was conducted based on the placebo-controlled subset of the safety population. As shown in Table 11, a total of 9 events occurred in the placebo-controlled subset of the safety population, with 6 reported in the linagliptin group and 3 reported in the placebo group.

Table 11: Summary of Events of Primary Composite Endpoint by Study and Treatment Group (Placebo-Controlled Subset of Safety Population)

Study	Arms	Sample Size	Primary Composite Endpoint n (%)	CV Death n (%)	Non-fatal MI n (%)	Non-fatal Stroke n (%)	US with Hosp* n (%)
1218.15	linagliptin	259	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
	placebo	130	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.16	linagliptin	336	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	placebo	167	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.17	linagliptin	523	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
	placebo	177	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
1218.18	linagliptin	792	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
	placebo	263	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
1218.23	linagliptin	319	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	placebo/ ***voglibose***	242	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.35	linagliptin	161	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
	placebo	84	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.50	linagliptin	151	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
	placebo	76	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

Source: Created by reviewer.

In the placebo-controlled subset of the safety population, the incidence of CV related events was not statistically significantly different between the linagliptin group and the placebo group (Table 12). The M-H risk difference between linagliptin and placebo was -0.04% with a 95% CI of (-0.45%, 0.37%). Compared to placebo, the M-H relative risk

ratio of linagliptin was 0.86 with a 95% CI of (0.23, 3.26), and the exact stratified odds ratio of linagliptin was 0.85 with a 95% CI of (0.18, 5.32).

Table 12: Sensitivity Meta-analysis Results of Primary Composite Endpoint (Placebo-Controlled Subset of Safety Population)

	Linagliptin	Placebo
Incidence of events	6/2541 (0.24%)	3/977 (0.31%)
M-H Risk Difference (95% CI)	-0.04% (-0.45%, 0.37%)	
M-H Relative Risk Ratio (95% CI)	0.86 (0.23, 3.26)	
Exact Stratified Odds Ratio (95% CI)	0.85 (0.18, 5.32)	

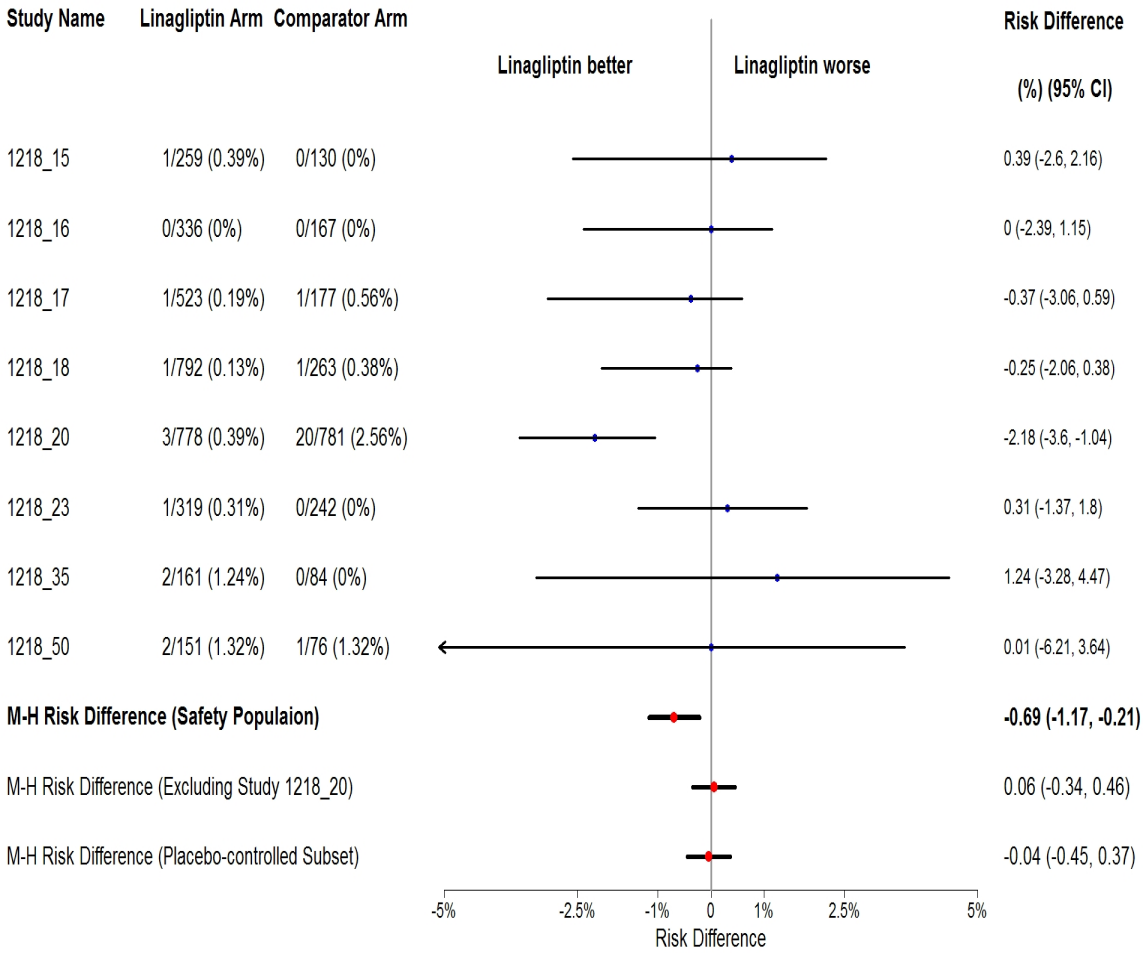
Source: Created by reviewer.

3.1.6.1.3 Forest Plot of All Results for Primary Composite Endpoint

The forest plot of the reviewer's analysis results of the primary composite endpoint based on risk difference is presented in Figure 2. Both the individual risk differences and the corresponding exact 95% CIs of each trial, and M-H risk difference results including the two sensitivity analyses are included in the forest plot. Among all the 8 randomized phase 3 trials, Study 1218.20 was the only one showing statistically significant difference between linagliptin and glimepiride within a trial, with an individual risk difference of -2.18% and an exact 95% CI of (-3.60%, -1.04%). Therefore, it was not surprising to find that Study 1218.20 had a high impact on the M-H risk difference results. After excluding Study 1218.20, the M-H risk difference changed from -0.69% with a 95% CI of (-1.17%, -0.21%) in the safety population to 0.06% with a 95% CI of (-0.34%, 0.46%) in the sensitivity analysis. Similarly, the comparison between linagliptin and placebo based on the placebo-controlled subset was very different from the comparison between linagliptin and all comparator based on the safety population (M-H risk difference of -0.04% versus -0.69%).

The forest plots of the reviewer's analysis results of the primary composite endpoint based on relative risk ratio or odds ratio are included in the Appendix.

Figure 2: Forest Plot of Reviewer's Analysis Results of Primary Composite Endpoint (Risk difference)



Source: Created by reviewer.

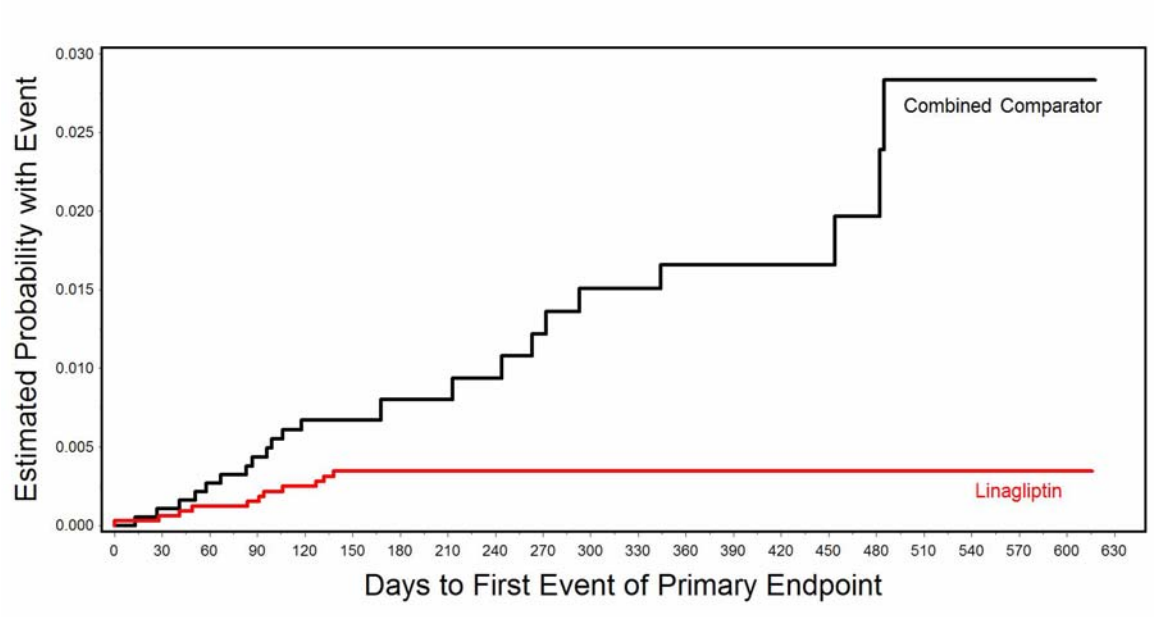
3.1.6.1.4 Time-to-Event Analysis of Primary composite endpoint

Based on the Kaplan Meier method using safety information from the 8 randomized phase 3 trials, the cumulative probability of developing a CV related event as measured by the primary composite endpoint is shown in Figure 3. In the combined comparator group, event of CV death, non-fatal MI, non-fatal stroke, or hospitalization due to unstable angina occurred earlier and more often than in the linagliptin group. Based on the stratified log-rank test stratified by trial, the onset time of event was statistically significantly different between the linagliptin group and the comparator group (p-value=0.003). The stratified Cox proportional hazard ratio (HR) of linagliptin compared to combined comparator was 0.35 with a 95% CI of (0.17, 0.73).

Reviewer's comment: *Because no event of the primary composite endpoint occurred in Study 1218.16, Study 1218.16 would not contribute to the stratified Cox regression model*

at all. The stratified HR result was based on the other 7 randomized phase 3 trials with at least one event.

Figure 3: Time to Event Analysis of the Primary Composite Endpoint (Safety Population, Double-Blind Treatment Phase)



Source: Created by reviewer.

3.1.6.1.5 Sensitivity Time-to-Event Analyses

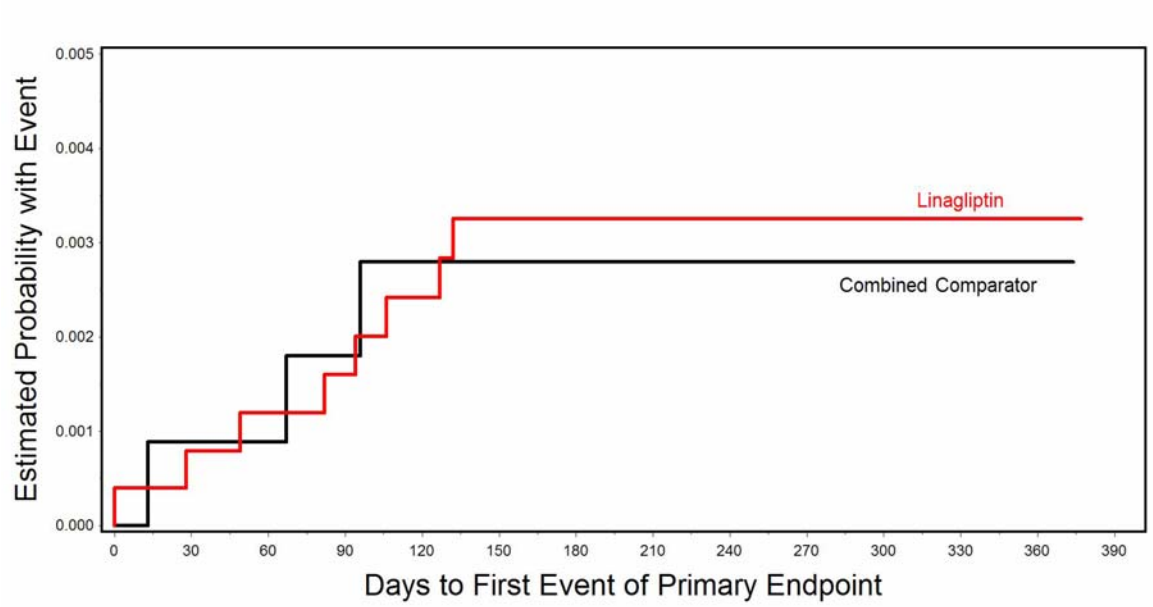
Excluding Study 1218.20

In order to evaluate the impact of Study 1218.20 on the time-to-event analysis result, the cumulative probability of developing a CV related event as measured by the primary composite endpoint is shown in Figure 4 using the 7 randomized phase 3 trials other than Study 1218.20. The Kaplan Meier curves of the combined comparator group and the linagliptin group are similar to each other. The stratified log-rank test, stratified by trial, showed that the onset time of event was not statistically significantly different between the linagliptin group and the comparator group (p-value=0.83). The stratified Cox proportional hazard ratio (HR) of linagliptin compared to combined comparator was 1.16 with a 95% CI of (0.31, 4.38).

Reviewer's comment: *The stratified HR result was based on the 6 randomized phase 3 trials with at least one event, not including Study 1218.16.*

Reviewer's comment: *The result of sensitivity analysis was very different from the result presented in Figure 3. This suggested that the analysis in Section 3.1.6.1.4 was heavily driven by Study 1218.20 and the pooled results might not be robust.*

Figure 4: Time to Event Analysis of the Primary Composite Endpoint Excluding Study 1218.20 (Safety Population, Double-Blind Treatment Phase)



Source: Created by reviewer.

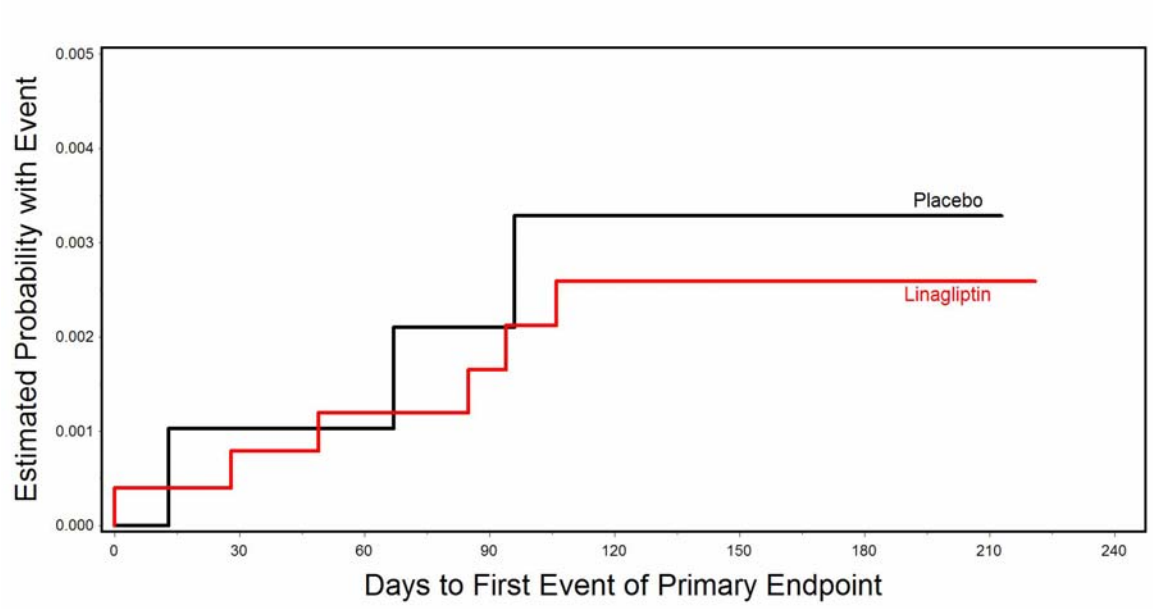
Placebo-Controlled Trials

It is also of clinical interest to make the direct comparison between linagliptin and placebo, rather than the comparison between linagliptin and combined comparator. Based on the 7 randomized placebo-controlled phase 3 trials (only the placebo-controlled phase), the cumulative probability of developing a CV related event as measured by the primary composite endpoint is shown in Figure 5. In the placebo group, CV related event appeared to occur earlier and more often than in the linagliptin group, while the Kaplan Meier curves of the placebo group and the linagliptin group were similar and crossed each other. The stratified log-rank test, stratified by trial, showed that the onset time of event was not statistically significantly different between the linagliptin group and the placebo group (p-value=0.81). The stratified Cox proportional hazard ratio (HR) of linagliptin compared to placebo was 0.84 with a 95% CI of (0.21, 3.38).

Reviewer's comment: *Study 1218.16 and Study 1218.23 did not contribute to the stratified HR result, because no event of the primary composite endpoint occurred in either of these two studies within the placebo-controlled phase. The stratified HR result was based on the other 5 randomized placebo-controlled phase 3 trials with at least one event.*

Reviewer's comment: *Only 9 events of the primary composite endpoint occurred during the placebo-controlled phase in these 7 placebo-controlled phase 3 trials. Because of the very small number of events, caution is needed when interpreting the time-to-event analysis results for the placebo-controlled trials.*

Figure 5: Time to Event Analysis of the Primary composite endpoint (Placebo-Controlled Trials, Safety Population, Double-Blind Placebo-Controlled Phase)



Source: Created by reviewer.

3.1.6.2 Secondary Endpoint

Besides the primary composite endpoint, several secondary endpoints were also evaluated in the safety population, which included FDA defined custom MACE (derived from 34 MedDRA preferred terms), as well as each component of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke, and hospitalization due to unstable angina.

The summary of custom MACE events is presented in Table 13. In the safety population, a total of 28 MACE events occurred, with 9 reported in the linagliptin group and 19 reported in the all comparator group. Similar as the primary composite endpoint, the majority of the MACE events occurred in the glimepiride group from Study 1218.20. The summary of CV death, non-fatal MI, non-fatal stroke, or hospitalization due to unstable angina is presented in Table 8 in Section 3.1.6.1.1.

Table 13: Summary of Events of MACE by Study and Treatment Group (Safety Population)

Study	Arms	Sample Size	MACE n (%)
1218.15	linagliptin	259	0 (0.0)
	placebo	130	0 (0.0)
1218.16	linagliptin	336	0 (0.0)
	placebo	167	0 (0.0)
1218.17	linagliptin	523	1 (0.2)
	placebo	177	0 (0.0)
1218.18	linagliptin	792	1 (0.1)
	placebo	263	1 (0.4)
1218.20	linagliptin	778	3 (0.4)
	glimepiride	781	15 (1.9)
1218.23	linagliptin	319	1 (0.3)
	placebo/***voglibose***	242	1 (0.4)
1218.35	linagliptin	161	1 (0.6)
	placebo	84	0 (0.0)
1218.50	linagliptin	151	2 (1.3)
	placebo	76	2 (2.6)

Source: Created by reviewer.

In the safety population, meta-analysis results of all secondary endpoints based on M-H risk difference and M-H relative risk ratio are presented in Table 14. Compared to the all comparator group, the CV risk of developing MACE was statistically lower in the linagliptin group. The M-H risk difference between linagliptin and all comparator was -0.58% with a 95% CI of (-1.02%, -0.14%), and the M-H relative risk ratio was 0.34 with a 95% CI of (0.16, 0.80).

Among the four components of the primary composite endpoint, statistically significant difference between linagliptin and all comparator was found for the risk of developing non-fatal stroke. Compared to the all comparator group, the M-H risk difference of linagliptin group was -0.43% with a 95% CI of (-0.74%, -0.12%), and the M-H relative risk ratio was 0.13 with a 95% CI of (0.03, 0.70). For each of other three components of the primary composite endpoint (CV death, non-fatal MI, or hospitalization due to unstable angina), the risk appeared to be lower in the linagliptin group as compared to the all comparator group, but no statistically significant difference was found. The corresponding M-H risk difference was -0.01%, -0.13%, and -0.12%, while the corresponding M-H relative risk ratio was 0.85, 0.59, and 0.19, respectively.

Table 14: Meta-Analysis Results of Secondary Endpoints (Safety Population)

	Linagliptin (N=3319)	All Comparator (N=1920)
Secondary Endpoint: MACE		
Events of MACE (%)	9 (0.27%)	19 (0.99%)
M-H Risk Difference (95% CI)	-0.58% (-1.02%, -0.14%)	
M-H Relative Risk Ratio (95% CI)	0.34 (0.15, 0.80)	
Secondary Endpoint: CV Death		
Events of CV Death (%)	2 (0.06%)	2 (0.10%)
M-H Risk Difference (95% CI)	-0.01% (-0.17%, 0.14%)	
M-H Relative Risk Ratio (95% CI)	0.85 (0.10, 6.96)	
Secondary Endpoint: Non-fatal MI		
Events of Non-fatal MI (%)	6 (0.18%)	7 (0.36%)
M-H Risk Difference (95% CI)	-0.13% (-0.41%, 0.15%)	
M-H Relative Risk Ratio (95% CI)	0.59 (0.18, 1.99)	
Secondary Endpoint: Non-fatal Stroke		
Events of Non-fatal Stroke (%)	2 (0.06%)	11 (0.57%)
M-H Risk Difference (95% CI)	-0.43% (-0.74%, -0.12%)	
M-H Relative Risk Ratio (95% CI)	0.13 (0.03, 0.70)	
Secondary Endpoint: Hospitalization due to unstable angina		
Events of UA Hospitalization (%)	1 (0.03%)	3 (0.16%)
M-H Risk Difference (95% CI)	-0.12% (-0.30%, 0.06%)	
M-H Relative Risk Ratio (95% CI)	0.19 (0.02, 2.20)	

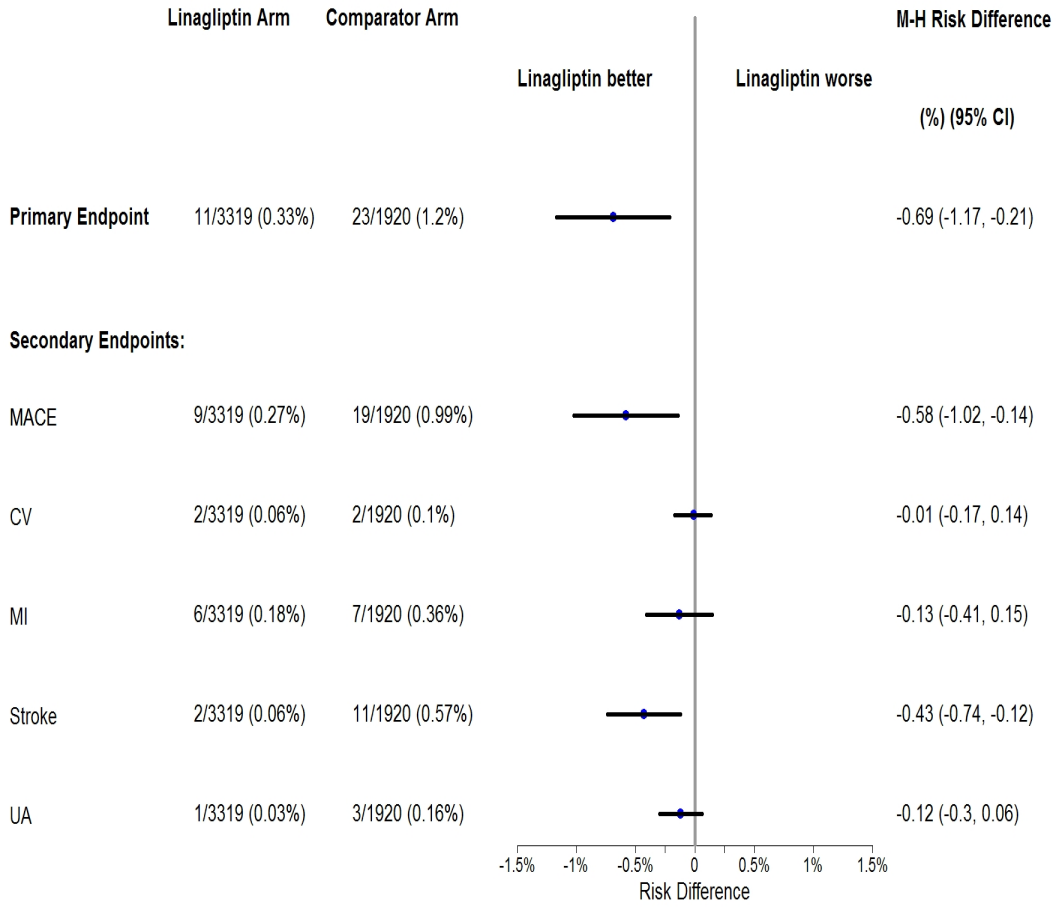
Source: Created by reviewer.

The forest plot of reviewer's analysis results of secondary endpoints based on risk difference is presented in Figure 6 (the forest plot for relative risk ratio is included in the Appendix), respectively. The results for MACE or non-fatal stroke were both similar to the results of the primary composite endpoint presented in Section 3.1.6.1.1. Results for other secondary endpoints (CV death, non-fatal MI, hospitalization due to unstable angina) were in the same direction of the primary composite endpoint, but did not reach statistical significance.

Reviewer's comment: *Because of the small number of events for the secondary endpoints (especially for CV death and hospitalization due to unstable angina)), the analyses should be considered as exploratory, and all the results should be interpreted with caution.*

Reviewer's comment: *Similar to the primary composite endpoint, the results of secondary endpoints were also heavily driven by Study 1218.20. Due to the small number of events, no sensitivity analysis was conducted for the secondary endpoints in the review.*

Figure 6: Forest Plot of Reviewer's Analysis Results of Secondary Endpoints (M-H Risk difference)



Source: Created by reviewer.

4 Findings in Special/Subgroup Populations

In the following sections, analysis results for CV related safety endpoints are presented for specific subgroups. It should be noted that these analyses are exploratory in nature to assess general trends. No protocol-defined multiplicity adjustments were provided and as such the statistical analysis does not include a multiplicity adjustment in the results that follow.

4.1 Gender, Race, and Age

Gender

Among the 5,239 subjects in the safety population, 2908 (55.5%) were male subjects and 2331 (44.5%) were female subjects. Among the 34 subjects reported with events of the primary composite endpoint, 27 were male subjects and 7 were female subjects (detailed summary of primary composite endpoint for each gender group is included in the Appendix).

Among male subjects, the risk of developing a CV related event as measured by the primary composite endpoint was statistically significantly lower in the linagliptin group than in the all comparator group. The corresponding M-H risk difference between linagliptin and all comparator was -1.20% with a 95% CI of (-1.95%, -0.44%). In contrast, among female subjects, the difference between the linagliptin group and the all comparator group was minimal and not statistically significant. The M-H risk difference between linagliptin and all comparator was 0.0% with a 95% CI of (-0.46%, 0.47%).

Reviewer's comment: *In the subgroup of female subjects, only 7 events of primary composite endpoint occurred. Because of the very small number of events, caution is needed when interpreting the results for the subgroup of female subjects.*

Race

Among the 5,239 subjects in the safety population, 3168 (69.5%) were White subjects, 77 (1.5%) were Black subjects, and 1994 (38.1%) were Asian subjects. Among the 34 subjects reported with events of primary composite endpoint, 30 were White subjects and 4 were Asian subjects (detailed summary of primary composite endpoint for each racial group is included in the Appendix). Since no event occurred among the Black subjects, the analysis was not available for this subgroup.

Among White subjects, the risk of developing a CV related event as measured by the primary composite endpoint was statistically significantly lower in the linagliptin group than in the all comparator group. The corresponding M-H risk difference between linagliptin and all comparator was -1.21% with a 95% CI of (-1.96%, -0.47%). In contrast, among Asian subjects, the risk was slightly higher in the linagliptin group than in the all comparator group, but the difference was not statistically significant. The M-H risk

difference between linagliptin and all comparator was 0.10% with a 95% CI of (-0.30%, 0.54%).

Reviewer's comment: *In the subgroup of Asian subjects, only 4 events of primary composite endpoint occurred. Because of the very small number of events, caution is needed when interpreting the results for the subgroup of Asian subjects.*

Age

Among the 5,239 subjects in the safety population, 1136 (21.7%) aged 50 years or younger, 2635 (50.3%) were between 51 and 64 years old, 1289 (24.6%) were between 65 and 74 years old, and 189 (3.6%) aged 75 years or older. Among the 34 subjects reported with events of the primary composite endpoint, 1 event occurred in subjects aged 50 years or younger, 14 events occurred in subjects aged between 51 and 64 years, 18 events occurred in subjects aged between 65 and 74 years, and 1 event occurred in subjects aged 75 years or older (detailed summary of primary composite endpoint for each age category is included in the Appendix).

Within each of the four age categories, the risk of developing a CV related event as measured by the primary composite endpoint appeared to be lower in the linagliptin group than in the all comparator group, but the difference between linagliptin and all comparator was not statistically significant except for the age category between 65 and 74 years. Among subjects between age of 65 and 74, the M-H risk difference between linagliptin and all comparator was -1.46% with a 95% CI of (-2.81%, -0.12%). For subjects in the other three age categories, the corresponding M-H risk difference between linagliptin and all comparator was -0.20%, -0.46%, and -1.43% for age 50 or younger, age between 51 and 64, and age 75 or older respectively.

4.2 Other Special/Subgroup Populations

4.2.1 Ethnicity

Among the 5,239 subjects in the safety population, 543 (10.4%) were of Hispanic or Latino ethnicity, and 4692 (89.3%) were of non Hispanic or Latino ethnicity. Among the 34 subjects reported with events of the primary composite endpoint, 2 events occurred in subjects classified as Hispanic or Latino, and 32 events occurred in subjects who were classified as non Hispanic or Latino (detailed summary of primary composite endpoint for each ethnic group is included in the Appendix).

Among non Hispanic or Latino subjects, the risk of developing a CV related event as measured by the primary composite endpoint was statistically significantly lower in the linagliptin group than in the all comparator group. The corresponding M-H risk difference between linagliptin and all comparator was -0.82% with a 95% CI of (-1.34%, -0.29%). In contrast, among Hispanic or Latino subjects, the CV risk of developing the primary composite endpoint was higher in the linagliptin group than in the all comparator

group, but the difference between linagliptin and all comparator was not statistically significant. The M-H risk difference was 0.54% with a 95% CI of (-0.21%, 1.29%).

4.2.2 Baseline BMI

Among the 5,239 subjects in the safety population, 3204 (61.2%) had baseline BMI below 30 kg/m^2, and 2035 (38.8%) had baseline BMI greater or equal to 30 kg/m^2. Among the 34 subjects reported with events of primary composite endpoint, 19 events occurred in subjects with baseline BMI below 30, and 15 events occurred in subjects with a baseline BMI greater or equal to 30 (detailed summary of primary composite endpoint for each category of baseline BMI is included in the Appendix).

Within each category, the risk of developing a CV related event as measured by the primary composite endpoint was statistically significantly lower in the linagliptin group than in the all comparator group. Among subjects with baseline BMI below 30, the M-H risk difference between linagliptin and all comparator was -0.64% with a 95% CI of (-1.24%, -0.03%). Similarly, among subjects with baseline BMI greater or equal to 30, the M-H risk difference between linagliptin and all comparator was -0.80% with a 95% CI of (-1.58%, -0.02%).

4.2.3 Baseline Renal Impairment Status

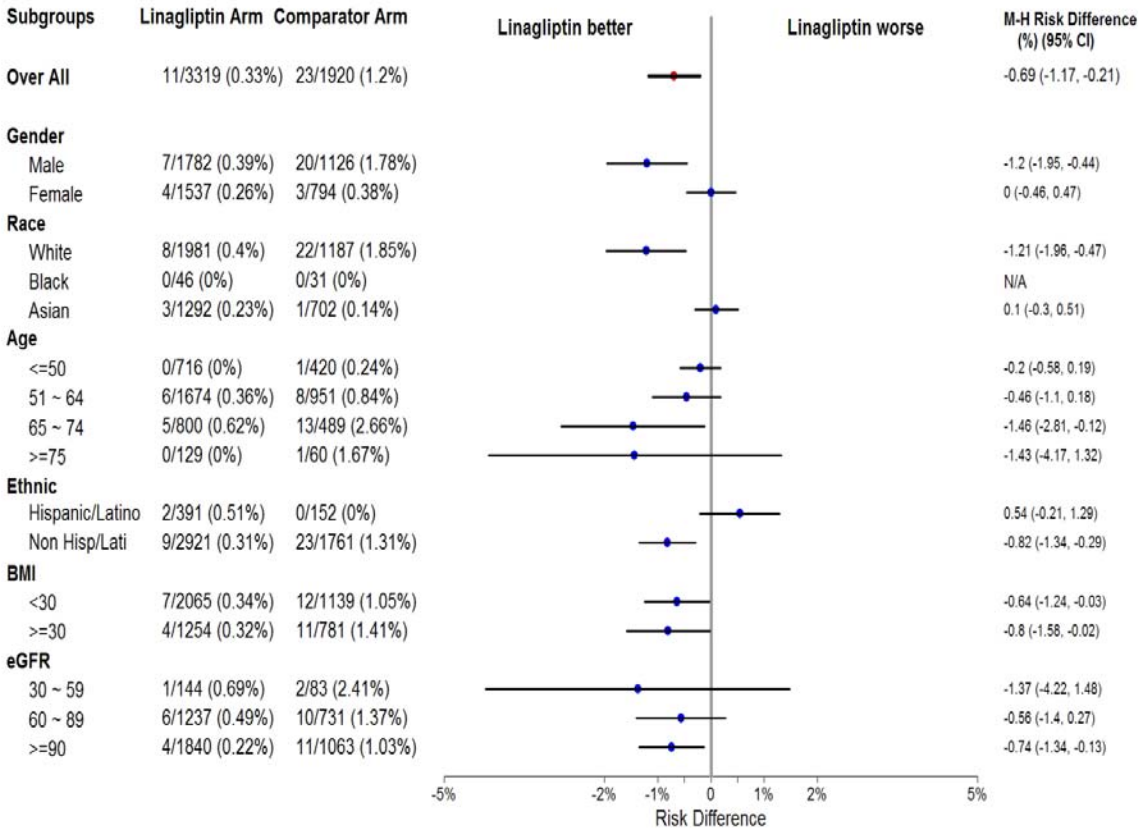
At baseline, subjects with estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min were considered to have moderate renal impairment, subjects with eGFR between 60 and 90 were considered to have mild renal impairment, and subjects with eGFR greater or equal to 90 mL/min were considered to have none renal impairment. Among the 5,239 subjects in the safety population, 227 (4.3%) had moderate renal impairment, 1968 (37.6%) had mild renal impairment, and 2903 (55.4%) had none renal impairment. Among the 34 subjects reported with events of primary composite endpoint, 3 events occurred in subjects with moderate renal impairment at baseline, 16 events occurred in subjects with mild renal impairment, and 15 events occurred in subjects with no renal impairment (detailed summary of primary composite endpoint for each category of baseline renal impairment status is included in the Appendix).

Within each of the three renal impairment categories, the risk of developing a CV related event as measured by the primary composite endpoint appeared to be lower in the linagliptin group than in the all comparator group, but the difference between linagliptin and all comparator was not statistically significant except for the category of no renal impairment. Among subjects with no renal impairment, the M-H risk difference between linagliptin and all comparator was -0.74% with a 95% CI of (-1.34%, -0.13%). The M-H risk difference between linagliptin and all comparator was -1.37% and -0.56%, for subjects with moderate renal impairment and subjects with mild renal impairment, respectively.

4.3 Summary Forest Plot for all Subgroup Analysis Results

The forest plot of reviewer's subgroup analysis results based on risk difference is presented in Figure 8 (forest plot based on relative risk ratio is included in the Appendix). Most of the subgroup analysis results were in the same direction as the overall result for the primary composite endpoint.

Figure 7: Forest Plot of Reviewer's Analysis Results of Subgroups (M-H Risk Difference)



* The 95% confidence intervals presented in the plot were obtained based on M-H risk difference approach.
Source: Created by reviewer.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary agreed upon safety endpoint was a composite endpoint made up by CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization due to unstable angina.

Phase 3 data from the 8 randomized studies were pooled to evaluate the risk of developing a CV related event as measured by the primary composite endpoint. In this review, the comparison of incidence between the linagliptin group and the pooled all comparator group (including comparators of glimepiride, voglibose, or placebo) was

performed using the Mantel-Haenszel (M-H) risk difference approach with study as stratification factor. The M-H relative risk ratio approach and the exact stratified odds ratio approach were also applied to evaluate the relative risk ratio or odds ratio of linagliptin. Stratified log-rank test and stratified Cox proportional hazards regression model were performed for the time-to-event analyses. More details for the statistical methodologies used in this review are provided in Section 3.1.2.

Based on the pooled data of all 8 randomized phase 3 trials, a total of 34 events of the primary composite endpoint were reported, 11 occurred in the linagliptin group and 23 occurred in the pooled all comparator group. The incidence of the primary composite endpoint was 0.33% (11/3319) in the linagliptin group, as compared to 1.20% (23/1920) in the all comparator group. The M-H risk difference between linagliptin and all comparator was -0.69% with a 95% confidence interval (CI) of (-1.17%, -0.21%). The M-H relative risk ratio between linagliptin and all comparator was 0.34 with a 95% CI of (0.15, 0.74), and similar results were seen for the exact stratified odds ratio. Detailed analysis results are provided in Section 3.1.6.1.1 and Section 3.1.6.1.4.

The meta-analysis results for the primary composite endpoint were heavily driven by Study 1218.20. Because Study 1218.20 had different trial design characteristics than the other 7 trials (the only glimepiride-controlled trial, the only non-inferiority trial, and had the longest duration), and the study population in Study 1218.20 appeared to have higher baseline CV risk than all other trials, the heavy impact of Study 1218.20 on the overall meta-analysis results is of concern. Among the total of 23 events of the primary composite endpoint reported in the pooled all comparator group, 20 occurred in the glimepiride arm in Study 1218.20. Therefore, two sensitivity analyses were performed to assess the robustness of the meta-analysis results. Without Study 1218.20, the incidence of the primary composite endpoint was 0.31% (8/2541) in the linagliptin group, as compared to 0.26% (3/1139) in the all comparator group. The M-H risk difference between linagliptin and all comparator was 0.06% with a 95% CI of (-0.34%, 0.46%), and the M-H relative risk ratio of linagliptin was 1.21 with a 95% CI of (0.35, 4.26). Furthermore, direct comparison between linagliptin and placebo was evaluated based on the placebo-controlled subset of the randomized phase 3 trials. The incidence rate of primary composite endpoint was 0.24% (6/2541) in the linagliptin group, as compared to 0.31% (3/977) in the placebo group. The M-H risk difference between linagliptin and placebo was -0.04% with a 95% CI of (-0.45%, 0.37%), and the M-H relative risk ratio of linagliptin was 0.86 with a 95% CI of (0.23, 3.26). Detailed sensitivity analysis results are provided in Section 3.1.6.1.2 and Section 3.1.6.2.4.

Several secondary endpoints were also evaluated in this review, including custom major adverse cardiovascular event (MACE) and each component of the primary composite endpoint. The results for MACE or non-fatal stroke were both close to the results for the primary composite endpoint. Results for other secondary endpoints (CV death, non-fatal MI, and hospitalization due to unstable angina) were in the same direction as the primary composite endpoint, but did not reach statistical significance. Detailed analysis results for the secondary endpoints are provided in Section 3.1.6.2.

The difference between linagliptin and all comparator in developing a CV related event as measured by the primary composite endpoint were also evaluated in several subgroups. Most of the subgroup analysis results were in the same direction as the overall result for the primary composite endpoint. Detailed results for subgroup analyses are provided in Section 4.

5.2 Conclusions and Recommendations

Among the 8 randomized phase 3 trials for linagliptin, the trial design characteristics of Study 1218.20 differed from the other 7 trials (the only glimepiride-controlled trial, the only non-inferiority trial, and had the longest duration), and the study population in Study 1218.20 appeared to have higher baseline CV risk than all other trials. Therefore, utilizing data from Study 1218.20 and its contribution to a meta-analysis may be problematic. Due to the fact that Study 1218.20 was the only glimepiride-controlled trial, extra caution is needed when interpreting the results of the comparison between the linagliptin group and the pooled all comparator group.

Based on the meta-analysis of all 8 randomized phase 3 trials, the incidence of CV related events measured utilizing an agreed upon primary composite CV safety endpoint (composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization due to unstable angina) was found to be statistically significantly lower in the linagliptin group than in the pooled all comparator group (glimepiride, voglibose, or placebo) at the nominal α=0.05 level. The M-H risk difference between linagliptin and all comparator was -0.69% with a 95% confidence interval of (-1.17%, -0.21%). However, the results of the meta-analysis were heavily driven by Study 1218.20. One sensitivity analysis showed that, without Study 1218.20, the incidence of the primary composite endpoint was higher in the linagliptin group than in the all comparator group (voglibose or placebo) but the difference was not statistically significant. The M-H risk difference between linagliptin and all comparator was 0.06% with a 95% CI of (-0.34%, 0.46%). Furthermore, based on the placebo-controlled subset of the trials, another sensitivity analysis found no statistically significant difference between linagliptin and placebo in the incidence of primary composite endpoint. The M-H risk difference between linagliptin and placebo was -0.04% with a 95% CI of (-0.45%, 0.37%).

In Study 1218.20 also, as compared to glimepiride, linagliptin was shown to be associated with statistically significantly lower risk in developing a CV related event as measured by the primary composite endpoint. The majority of events observed in the phase 3 program for linagliptin were from Study 1218.20 and this in turn impacted the meta-analysis of the 8 trials comparing linagliptin to all comparators. Therefore, no definite conclusion can be reached on the CV safety of linagliptin in relation to a placebo or alternative active control other than glimepiride.

Appendix

A.1 Supplementary Tables

A.1.1 Summary of Primary Composite Endpoint by Subgroup

Table 15: Summary of Events of Primary Composite Safety Endpoint by Gender, Study and Treatment Group (Safety Population)

Gender=Male (Total=2908)								
	Study 1218.15 (N=237)		**Study 1218.16 (N=243)**		**Study 1218.17 (N=379)**		**Study 1218.18 (N=498)**	
Primary composite endpoint n (%)	**BI 1536** n=152	**Control** n=85	**BI 1536** n=164	**Control** n=79	**BI 1536** n=278	**Control** n=101	**BI 1536** n=371	**Control** n=127
	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.0)	1 (0.3)	1 (0.8)
	Study 1218.20 (N=939)		**Study 1218.23 (N=395)**		**Study 1218.35 (N=129)**		**Study 1218.50 (N=88)**	
Primary composite endpoint n (%)	**BI 1536** n=462	**Control** n=477	**BI 1536** n=223	**Control** n=172	**BI 1536** n=77	**Control** n=52	**BI 1536** n=55	**Control** n=33
	1 (0.2)	17 (3.6)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	1 (3.0)
Gender=Female (Total=2331)								
	Study 1218.15 (N=152)		**Study 1218.16 (N=260)**		**Study 1218.17 (N=321)**		**Study 1218.18 (N=557)**	
Primary composite endpoint n (%)	**BI 1536** n=107	**Control** n=45	**BI 1536** n=172	**Control** n=88	**BI 1536** n=245	**Control** n=76	**BI 1536** n=421	**Control** n=136
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0
	Study 1218.20 (N=620)		**Study 1218.23 (N=166)**		**Study 1218.35 (N=116)**		**Study 1218.50 (N=139)**	
Primary composite endpoint n (%)	**BI 1536** n=316	**Control** n=304	**BI 1536** n=96	**Control** n=70	**BI 1536** n=84	**Control** n=32	**BI 1536** n=96	**Control** n=43
	2 (0.6)	3 (1.0)	0 (0.0	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Created by reviewer.

Table 16: Summary of Events of Primary Composite Safety Endpoint by Race, Study and Treatment Group (Safety Population)

Race=White (Total=3168)								
	Study 1218.15 (N=290)		**Study 1218.16 (N=270)**		**Study 1218.17 (N=533)**		**Study 1218.18 (N=492)**	
Primary composite endpoint n (%)	**BI 1536** n=193	**Control** n=97	**BI 1536** n=180	**Control** n=90	**BI 1536** n=393	**Control** n=140	**BI 1536** n=376	**Control** n=116
	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.7)	1 (0.3)	1 (0.9)
	Study 1218.20 (N=1319)		**Study 1218.23 (N=0)**		**Study 1218.35 (N=107)**		**Study 1218.50 (N=157)**	
Primary composite endpoint n (%)	**BI 1536** n=660	**Control** n=659	**BI 1536** n=0	**Control** n=0	**BI 1536** n=73	**Control** n=34	**BI 1536** n=106	**Control** n=51
	3 (0.5)	20 (3.0)	0 (0.0)	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gender=Black (Total=77)								
	Study 1218.15 (N=0)		**Study 1218.16 (N=0)**		**Study 1218.17 (N=9)**		**Study 1218.18 (N=8)**	
Primary composite endpoint n (%)	**BI 1536** n=0	**Control** n=0	**BI 1536** n=0	**Control** n=0	**BI 1536** n=7	**Control** n=2	**BI 1536** n=6	**Control** n=2
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0
	Study 1218.20 (N=38)		**Study 1218.23 (N=0)**		**Study 1218.35 (N=17)**		**Study 1218.50 (N=5)**	
Primary composite endpoint n (%)	**BI 1536** n=20	**Control** n=18	**BI 1536** n=0	**Control** n=0	**BI 1536** n=11	**Control** n=6	**BI 1536** n=2	**Control** n=3
	2 (0.6)	3 (1.0)	0 (0.0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gender=Asian (Total=1994)								
	Study 1218.15 (N=99)		**Study 1218.16 (N=233)**		**Study 1218.17 (N=158)**		**Study 1218.18 (N=555)**	
Primary composite endpoint n (%)	**BI 1536** n=66	**Control** n=33	**BI 1536** n=156	**Control** n=77	**BI 1536** n=123	**Control** n=35	**BI 1536** n=410	**Control** n=145
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0
	Study 1218.20 (N=202)		**Study 1218.23 (N=561)**		**Study 1218.35 (N=121)**		**Study 1218.50 (N=65)**	
Primary composite endpoint n (%)	**BI 1536** n=98	**Control** n=104	**BI 1536** n=319	**Control** n=242	**BI 1536** n=77	**Control** n=44	**BI 1536** n=43	**Control** n=22
	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	1 (4.6)

Source: Created by reviewer.

Table 17: Summary of Events of Primary composite endpoint by Age Categories, Study and Treatment Group (Safety Population)

Age ≤50 (Total=1136)								
	Study 1218.15 (N=86)		**Study 1218.16 (N=150)**		**Study 1218.17 (N=186)**		**Study 1218.18 (N=226)**	
Primary composite endpoint N (%)	**BI 1536** n=54	**Control** n=32	**BI 1536** n=97	**Control** n=53	**BI 1536** n=138	**Control** n=48	**BI 1536** n=163	**Control** n=63
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0))	0 (0.0)	0 (0.0)
	Study 1218.20 (N=262)		**Study 1218.23 (N=100)**		**Study 1218.35 (N=63)**		**Study 1218.50 (N=63)**	
Primary composite endpoint N (%)	**BI 1536** n=131	**Control** n=131	**BI 1536** n=51	**Control** n=49	**BI 1536** n=39	**Control** n=24	**BI 1536** n=43	**Control** n=20
	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
51≤ Age ≤64 (Total=2625)								
	Study 1218.15 (N=204)		**Study 1218.16 (N=248)**		**Study 1218.17 (N=360)**		**Study 1218.18 (N=541)**	
Primary composite endpoint N (%)	**BI 1536** n=141	**Control** n=63	**BI 1536** n=161	**Control** n=87	**BI 1536** n=272	**Control** n=88	**BI 1536** n=412	**Control** n=129
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.1)	1 (0.2)	1 (0.8)
	Study 1218.20 (N=791)		**Study 1218.23 (N=248)**		**Study 1218.35 (N=127)**		**Study 1218.50 (N=106)**	
Primary composite endpoint N (%)	**BI 1536** n=396	**Control** n=395	**BI 1536** n=139	**Control** n=109	**BI 1536** n=81	**Control** n=46	**BI 1536** n=72	**Control** n=34
	1 (0.3)	5 (1.3)	0 (0.0	0 (0.0)	2 (2.5)	0 (0.0)	1 (1.4)	1 (2.9)
65≤ Age ≤74 (Total=1289)								
	Study 1218.15 (N=88)		**Study 1218.16 (N=97)**		**Study 1218.17 (N=133)**		**Study 1218.18 (N=242)**	
Primary composite endpoint N (%)	**BI 1536** n=58	**Control** n=30	**BI 1536** n=71	**Control** n=26	**BI 1536** n=98	**Control** n=35	**BI 1536** n=179	**Control** n=63
	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0
	Study 1218.20 (N=440)		**Study 1218.23 (N=189)**		**Study 1218.35 (N=49)**		**Study 1218.50 (N=51)**	
Primary composite endpoint N (%)	**BI 1536** n=216	**Control** n=224	**BI 1536** n=109	**Control** n=80	**BI 1536** n=38	**Control** n=11	**BI 1536** n=31	**Control** n=20
	2 (0.9)	13 (5.8)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)
75≤ Age (Total=189)								
	Study 1218.15 (N=11)		**Study 1218.16 (N=8)**		**Study 1218.17 (N=21)**		**Study 1218.18 (N=46)**	
Primary composite endpoint N (%)	**BI 1536** n=6	**Control** n=5	**BI 1536** n=7	**Control** n=1	**BI 1536** n=15	**Control** n=6	**BI 1536** n=38	**Control** n=8
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0
	Study 1218.20 (N=66)		**Study 1218.23 (N=24)**		**Study 1218.35 (N=6)**		**Study 1218.50 (N=7)**	
Primary composite endpoint N (%)	**BI 1536** n=35	**Control** n=31	**BI 1536** n=20	**Control** n=4	**BI 1536** n=3	**Control** n=3	**BI 1536** n=5	**Control** n=2
	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Created by reviewer.

Table 18: Summary of Events of Primary composite endpoint by Ethnicity, Study and Treatment Group (Safety Population)

Hispanic or Latino (Total=543)								
	Study 1218.15 (N=21)		**Study 1218.16 (N=10)**		**Study 1218.17 (N=147)**		**Study 1218.18 (N=2388)**	
Primary composite endpoint n (%)	**BI 1536** n=12	**Control** n=9	**BI 1536** n=6	**Control** n=4	**BI 1536** n=113	**Control** n=34	**BI 1536** n=180	**Control** n=58
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
	Study 1218.20 (N=40)		**Study 1218.23 (N=0)**		**Study 1218.35 (N=42)**		**Study 1218.50 (N=45)**	
Primary composite endpoint n (%)	**BI 1536** n=21	**Control** n=19	**BI 1536** n=0	**Control** n=0	**BI 1536** n=28	**Control** n=14	**BI 1536** n=31	**Control** n=14
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Non Hispanic or Latino (Total=4682)								
	Study 1218.15 (N=366)		**Study 1218.16 (N=493)**		**Study 1218.17 (N=545)**		**Study 1218.18 (N=815)**	
Primary composite endpoint n (%)	**BI 1536** n=246	**Control** n=120	**BI 1536** n=330	**Control** n=163	**BI 1536** n=406	**Control** n=139	**BI 1536** n=611	**Control** n=204
	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.7)	0 (0.0)	1 (0.5)
	Study 1218.20 (N=1517)		**Study 1218.23 (N=561)**		**Study 1218.35 (N=203)**		**Study 1218.50 (N=182)**	
Primary composite endpoint n (%)	**BI 1536** n=756	**Control** n=761	**BI 1536** n=319	**Control** n=242	**BI 1536** n=133	**Control** n=70	**BI 1536** n=120	**Control** n=62
	3 (0.4)	20 (2.6)	1 (0.3)	0 (0.0)	1 (0.8)	0 (0.0)	2 (1.7)	1 (1.6)

* Ethnicity information was unknown for 14 subjects because of missingness.
Source: Created by reviewer.

Table 19: Summary of Events of Primary composite endpoint by Baseline BMI, Study and Treatment Group (Safety Population)

BMI < 30 kg/ m^2 (Total=3204)								
	Study 1218.15 (N=225)		**Study 1218.16 (N=302)**		**Study 1218.17 (N=393)**		**Study 1218.18 (N=717)**	
Primary composite endpoint N (%)	**BI 1536** n=157	**Control** n=68	**BI 1536** n=201	**Control** n=101	**BI 1536** n=295	**Control** n=98	**BI 1536** n=532	**Control** N=185
	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (1.0)	1 (0.2)	1 (0.5)
	Study 1218.20 (N=770)		**Study 1218.23 (N=506)**		**Study 1218.35 (N=162)**		**Study 1218.50 (N=129)**	
Primary composite endpoint N (%)	**BI 1536** n=396	**Control** n=374	**BI 1536** n=288	**Control** n=218	**BI 1536** n=106	**Control** n=56	**BI 1536** n=90	**Control** n=39
	1 (0.3)	9 (2.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	1 (2.6)
BMI ≥ 30 kg/ m^2 (Total=2035)								
	Study 1218.15 (N=164)		**Study 1218.16 (N=201)**		**Study 1218.17 (N=307)**		**Study 1218.18 (N=338)**	
Primary composite endpoint N (%)	**BI 1536** n=102	**Control** n=62	**BI 1536** n=135	**Control** n=66	**BI 1536** n=228	**Control** n=79	**BI 1536** n=260	**Control** n=78
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Study 1218.20 (N=789)		**Study 1218.23 (N=55)**		**Study 1218.35 (N=83)**		**Study 1218.50 (N=98)**	
Primary composite endpoint N (%)	**BI 1536** n=382	**Control** n=407	**BI 1536** n=31	**Control** n=24	**BI 1536** n=55	**Control** n=28	**BI 1536** n=61	**Control** n=37
	2 (0.5)	11 (2.7)	0 (0.0	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Created by reviewer.

Table 20: Summary of Events of Primary composite endpoint by Baseline Renal Impairment Status, Study and Treatment Group (Safety Population)

Moderate Renal Impairment: 30 ≤ eGFR (MDRD) <60 mL/min (Total=227)								
	Study 1218.15 (N=17)		**Study 1218.16 (N=18)**		**Study 1218.17 (N=23**		**Study 1218.18 (N=53)**	
Primary composite endpoint N (%)	**BI 1536** n=12	**Control** n=5	**BI 1536** n=14	**Control** n=4	**BI 1536** n=18	**Control** n=5	**BI 1536** n=37	**Control** n=16
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0))	0 (0.0)	0 (0.0)
	Study 1218.20 (N=73)		**Study 1218.23 (N=8)**		**Study 1218.35 (N=14)**		**Study 1218.50 (N=21)**	
Primary composite endpoint N (%)	**BI 1536** n=35	**Control** n=38	**BI 1536** n=6	**Control** n=2	**BI 1536** n=7	**Control** n=7	**BI 1536** n=15	**Control** n=6
	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Mild Renal Impairment: 60≤ eGFR (MDRD) <90 mL/min (Total=1968)								
	Study 1218.15 (N=152)		**Study 1218.16 (N=248)**		**Study 1218.17 (N=238)**		**Study 1218.18 (N=365)**	
Primary composite endpoint N (%)	**BI 1536** n=97	**Control** n=55	**BI 1536** n=165	**Control** N=83	**BI 1536** n=183	**Control** n=55	**BI 1536** n=282	**Control** n=83
	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
	Study 1218.20 (N=702)		**Study 1218.23 (N=91)**		**Study 1218.35 (N=94)**		**Study 1218.50 (N=78)**	
Primary composite endpoint N (%)	**BI 1536** n=341	**Control** n=361	**BI 1536** n=48	**Control** n=43	**BI 1536** n=67	**Control** n=27	**BI 1536** n=54	**Control** n=24
	3 (0.9)	10 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
None Renal Impairment: 90 mL/min ≤ eGFR (MDRD) (Total=2903)								
	Study 1218.15 (N=204)		**Study 1218.16 (N=217)**		**Study 1218.17 (N=414)**		**Study 1218.18 (N=601)**	
Primary composite endpoint n (%)	**BI 1536** n=140	**Control** n=64	**BI 1536** n=141	**Control** n=76	**BI 1536** n=302	**Control** n=112	**BI 1536** n=443	**Control** n=158
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.9)	0 (0.0)	1 (0.6)
	Study 1218.20 (N=746)		**Study 1218.23 (N=462)**		**Study 1218.35 (N=132)**		**Study 1218.50 (N=127)**	
Primary composite endpoint n (%)	**BI 1536** n=385	**Control** n=361	**BI 1536** n=265	**Control** n=197	**BI 1536** n=83	**Control** n=49	**BI 1536** n=81	**Control** n=46
	0 (0.0)	8 (2.2)	1 (0.4)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	1 (2.2)

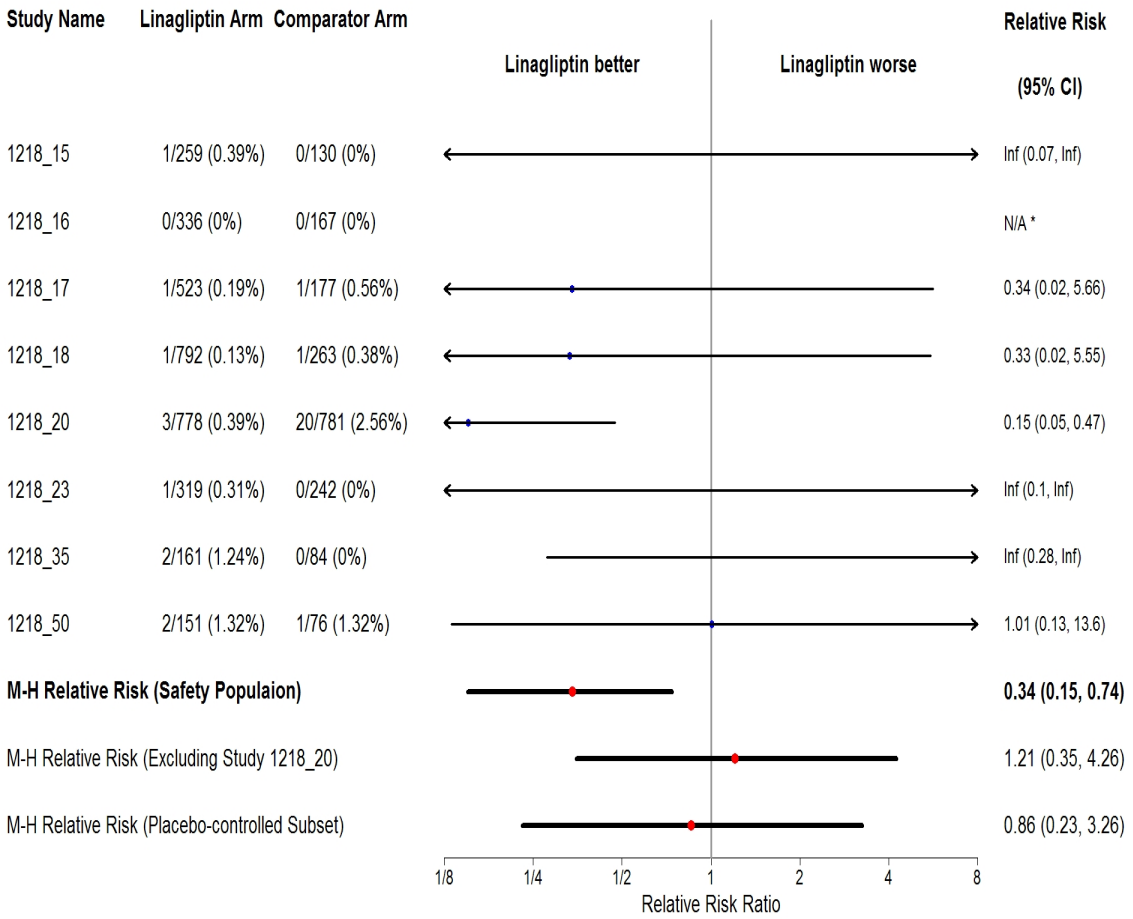
* Baseline renal impairment status were unknown for 141 subjects because of missing eGFR values.
Source: Created by reviewer.

A.2 Supplementary Figures

A.2.1 Additional forest plot of the primary composite endpoint

The forest plot of the reviewer's analysis results of the primary composite endpoint based on relative risk ratio is presented in Figure 8. Similarly, Study 1218.20 was the only one showing statistically significant difference between linagliptin and glimepiride, with individual relative risk ratio of 0.15and an exact 95% CI of (0.05, 0.47). With the exclusion of Study 1218.20, the M-H relative risk changed from 0.34 with a 95% CI of (0.15, 0.74) in the safety population to 1.21 with a 95% CI of (0.35, 4.26) in the sensitivity analysis. The comparison between linagliptin and placebo based on the placebo-controlled subset was also very different from the comparison between linagliptin and all comparator based on the safety population (M-H relative risk of 0.34 versus 0.86).

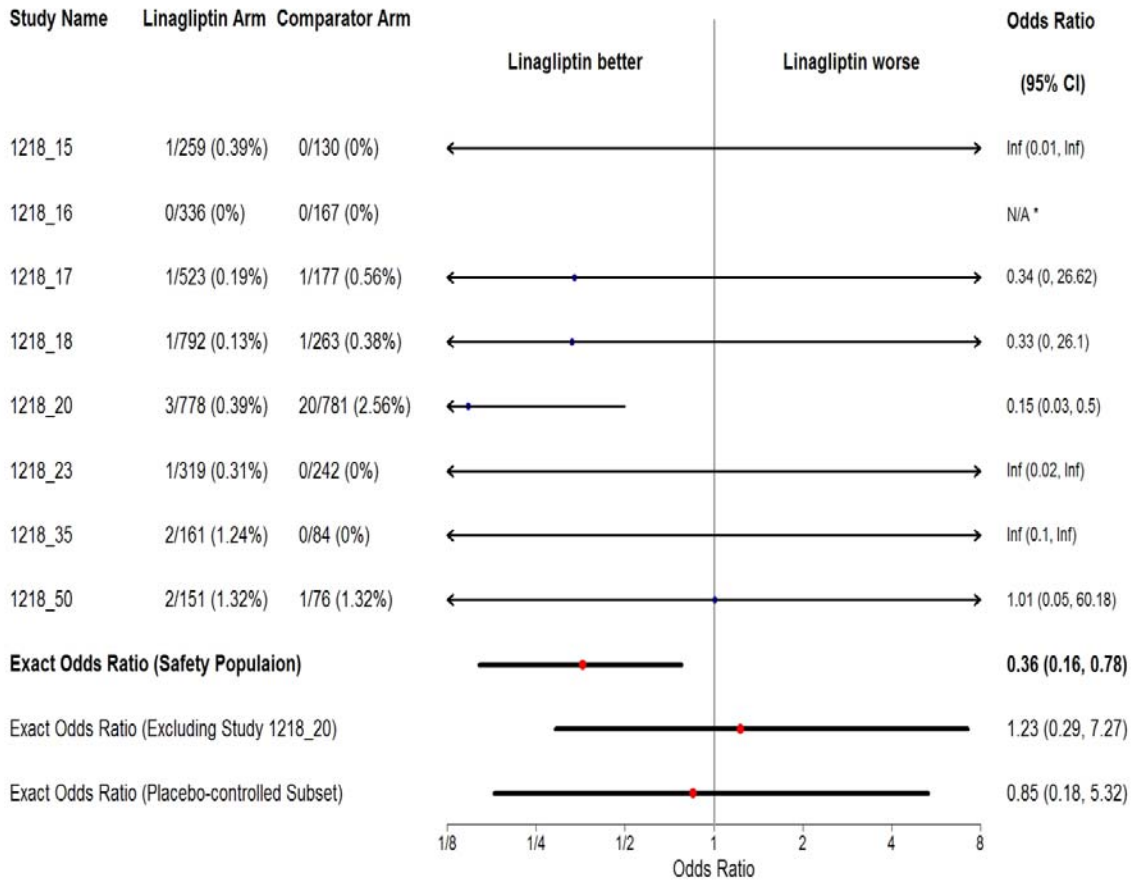
Figure 8: Forest Plot of Reviewer's Analysis Results of Primary composite endpoint (M-H Relative Risk)



* Study 1218.16 did not contribute to the M-H relative risk estimate, and did not have individual relative risk estimate with corresponding CI.
Source: Created by reviewer.

The forest plot of the reviewer's analysis results of the primary composite endpoint based on odds ratio is presented in Figure 9. Again, Study 1218.20 was the only study showing statistically significant difference between linagliptin and glimepiride, with individual odds ratio of 0.15 and an exact 95% CI of (0.03, 0.50). With the exclusion of Study 1218.20, the exact stratified odds ratio changed from 0.36 with a 95% CI of (0.16, 0.78) in the safety population to 1.23 with a 95% CI of (0.29, 7.27) in the sensitivity analysis. The comparison between linagliptin and placebo based on the placebo-controlled subset was also very different from the comparison between linagliptin and all comparator based on the safety population (exact stratified odds ratio of 0.36 versus 0.85).

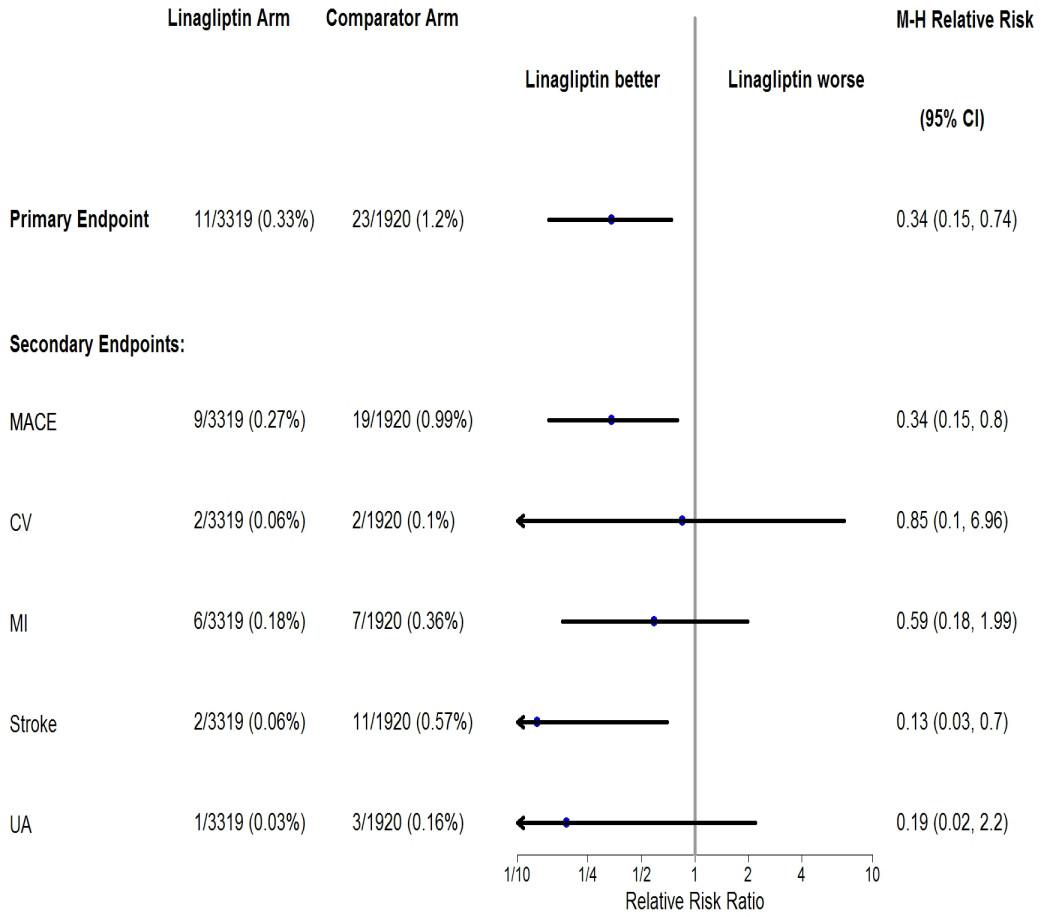
Figure 9: Forest Plot of Reviewer's Analysis Results of Primary composite endpoint (Exact Odds Ratio)



* Study 1218.16 did not contribute to the Exact Odds Ratio estimate, and it did not have individual odds ratio estimate with corresponding CI.
Source: Created by reviewer.

A.2.2 Additional forest plot of the secondary endpoints

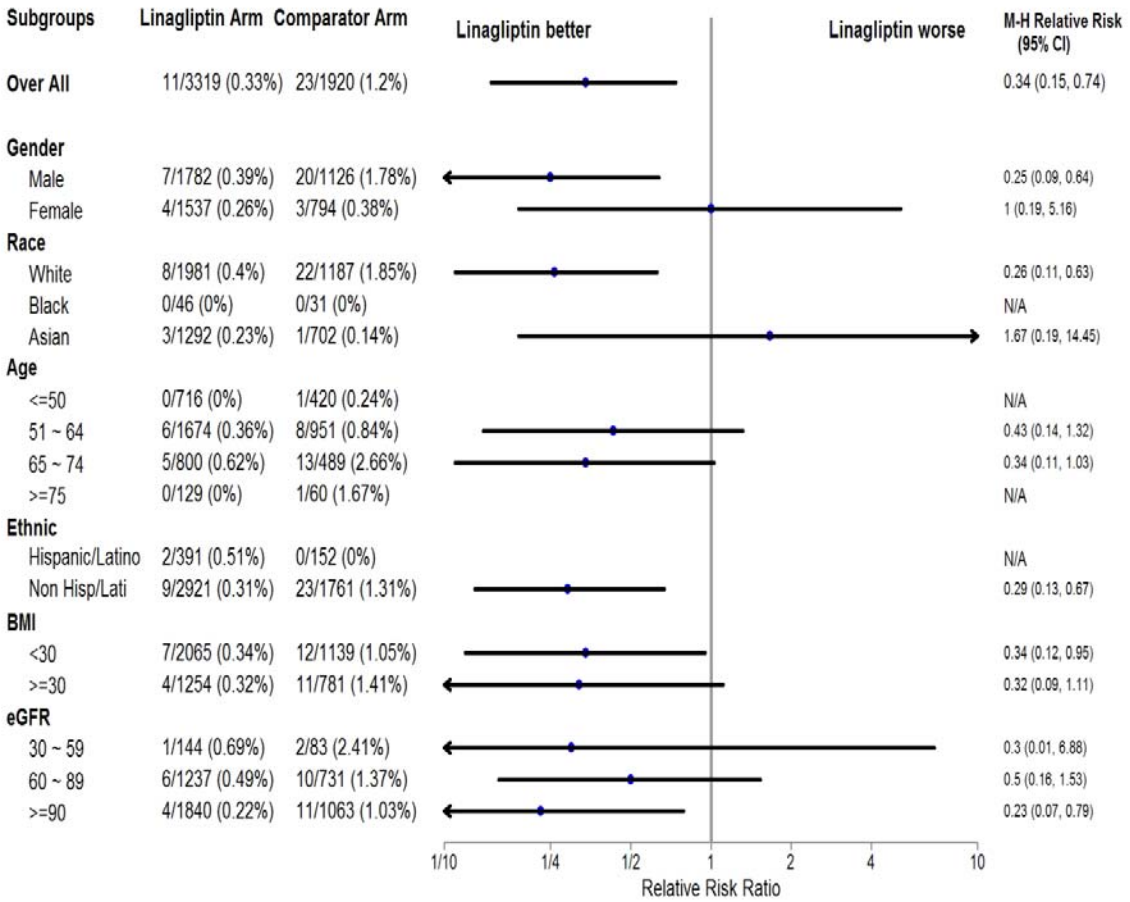
Figure 10: Forest Plot of Reviewer's Analysis Results of Secondary Endpoints (M-H Relative Risk)



Source: Created by reviewer.

A.2.3 Additional forest plot of subgroup analysis results

Figure 11: Forest Plot of Reviewer's Analysis Results of Subgroups (M-H Relative Risk)



Source: Created by reviewer.

Signatures/Distribution List

Primary Statistical Reviewer: Xiao Ding, PhD
Date: March 14, 2011

Concurring Reviewer(s):
Statistical Team Leader: Mat Soukup, PhD

Biometrics Division Director: Aloka Chakravarty, PhD

cc:

Archival NDA 201280
DMEP (HFD-510)/ Raymond Chiang, MS
DMEP (HFD-510)/ Somya (Verma) Dunn, MD
DMEP (HFD-510)/Ilan Irony, MD
DB7 (HFD-700)/Xiao Ding, PhD
DB7 (HFD-700)/Mat Soukup, PhD
DB7 (HFD-700)/Mark Levenson, PhD
DB7 (HFD-700)/Aloka Chakravarty, PhD
OB/IO (HFD-700)/Lillian Patrician, MS

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

/s/

XIAO DING
03/14/2011

MATTHEW J SOUKUP
03/14/2011
Concur with review

ALOKA G CHAKRAVARTY
03/14/2011

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/Serial Number:	20-1280/00
Drug Name:	Linagliptin
Indication(s):	To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise
Applicant:	Boehringer Ingelheim
Date(s):	Received 7/2/2010
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Wei Liu, Ph.D.
Concurring Reviewer:	J. Todd Sahlroot, Ph.D. (Deputy Director)
Medical Division:	Metabolism and Endocrinological Products (HFD-510, DMEP)
Clinical Team:	Somya V. Dunn, M.D. Ilan Irony, M.D. (Team Leader)
Project Manager:	Chiang, Raymond

Keywords: NDA review, clinical studies,

Table of Contents

LIST OF TABLES (OPTIONAL) **3**

LIST OF FIGURES (OPTIONAL) **4**

1. EXECUTIVE SUMMARY **6**

1.1 CONCLUSIONS AND RECOMMENDATIONS 6
1.1.1 Efficacy Conclusions: *6*
1.1.2 Safety Conclusion: *6*
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES 7
1.3 STATISTICAL ISSUES AND FINDINGS 8

2. INTRODUCTION **8**

2.1 OVERVIEW 8
2.2 DATA SOURCES 8

3. STATISTICAL EVALUATION **8**

3.1 EVALUATION OF EFFICACY 8
3.1.1 Monotherapy Trials *9*
3.1.2 Add-On Trials *19*
3.2 EVALUATION OF SAFETY 44

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS **45**

5. SUMMARY AND CONCLUSIONS **46**

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 46
5.2 CONCLUSIONS AND RECOMMENDATIONS 46
5.3 LABELLING COMMENTS 47

APPENDIX **48**

APPENDIX I: LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 48
APPENDIX II: SAF-2 TIME COURSE PLOTS OF SELECTED SAFETY ENDPOINTS 50
APPENDIX III: SAF-4 TIME COURSE PLOTS OF SELECTED SAFETY ENDPOINTS 57
APPENDIX IV: FOREST PLOT OF POOLED PIVOTAL STUDIES 63

Reference ID: 2917049

LIST OF TABLES (Optional)

Table 3.1. Summary of Clinical Trials Designed to Assess Safety and Efficacy 7
Table 3.1.1. Randomized, double-blend monotherapy trials 9
Table 3.1.2. Patient disposition for monotherapy trials 10
Table 3.1.3. Baseline demographics for monotherapy trials 10
Table 3.1.4. Glycemic Parameters in Placebo-Controlled Monotherapy Study 16 at Week 24 12
Table 3.1.5. Glycemic Parameters in Placebo-Controlled Monotherapy Study 50 at Week 18 16
Table 3.1.6. Randomized, double-blend add-on trials 19
Table 3.1.7. Patient disposition for add-on trials 19
Table 3.1.8. Baseline demographics for all randomized and treated patients in add-on trials 20
Table 3.1.9. Glycemic Parameters in Placebo-Controlled Add-on Study 17 at Week 24 22
Table 3.1.10. Glycemic Parameters in active-Controlled Add-on Study 20 at Week 52 27
Table 3.1.11. Glycemic Parameters in Placebo-Controlled Add-on to Pioglitazone Study 15 at Week 24 31
Table 3.1.12. SAS Output of the Type 3 Tests of Fixed Effects of the Model Containing Sex and Sex-Treatment Interaction Terms for Study 15 34
Table 3.1.13. Glycemic Parameters in Placebo-Controlled Sulphonylurea Add-on Study 35 at Week 18 35
Table 3.1.14. SAS Output of the Type 3 Tests of Fixed Effects of the Model Containing Sex and Sex-Treatment Interaction Terms for Study 35 39
Table 3.1.15. Glycemic Parameters in Placebo-Controlled Add-on Study 18 at Week 24 41
Table 3.2.1. Summary of SAF-2 Data Information 44
Table 3.2.2. Summary of SAF-4 Data Information 44

Reference ID: 2917049

LIST OF FIGURES (Optional)

Figure 3.1.1. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo for Study 16 (OC population). 11
Figure 3.1.2. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 16. 13
Figure 3.1.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 16 at Week 24. 13
Figure 3.1.4. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 16 by Subgroups. 14
Figure 3.1.5. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo for Study 50 (OC population). 15
Figure 3.1.6. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 50. 17
Figure 3.1.7. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 50 at Week 18. 17
Figure 3.1.8. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 50 by Subgroups. 18
Figure 3.1.9. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo for Study 17 (OC population). 21
Figure 3.1.10. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 17. 23
Figure 3.1.11. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 17 at Week 24. 23
Figure 3.1.12. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 17 by Subgroups. 24
Figure 3.1.13. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Glimepiride for Study 20 (OC data of FAS population). 25
Figure 3.1.14. The Time-course of HbA1c Difference between Linagliptin and Glimepiride Treatments in Study 20. 28
Figure 3.1.15. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and Glimepiride Treatments in Study 20 at Week 52. 28
Figure 3.1.16. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and Glimepiride Treatments in Study 20 by Subgroups. 29
Figure 3.1.17. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo in the Pioglitazone Add-on Study 15 (OC data of FAS population). 30
Figure 3.1.18. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in the Pioglitazone Add-on Study 15 at Week 24. 32
Figure 3.1.19. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 15 32
Figure 3.1.20. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 15 by Subgroups. 33
Figure 3.1.21. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 15. 34
Figure 3.1.22. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo as Add-on to Sulphonylurea for Study 35 (OC data of FAS population). 35
Figure 3.1.23. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments as Add-on to Sulphonylurea of Study 35 (OC data of FAS population). 37
Figure 3.1.24. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 35 at Week 18. 37
Figure 3.1.25. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 35 by Subgroups. 38
Figure 3.1.26. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 35. 39

Reference ID: 2917049

Figure 3.1.27. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo as Add-on to Metformin and Sulphonylurea for Study 18 (OC data of FAS population). 40
Figure 3.1.28. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 18. 42
Figure 3.1.29. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 18 at Week 24. 42
Figure 3.1.30. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments as Add-on to Metformin and Sulphonylurea in Study 18 by Subgroups. 43

Appendix Figures

SAF-2 Figure 1. The Time Course of Amylase (U/L) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients. 50
SAF-2 Figure 2. The Time Course of Creatine (mg/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients. 51
SAF-2 Figure 3. The Time Course of Creatine Kinase (U/L) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients. 52
SAF-2 Figure 4. The Time Course of LDL Cholesterol (mg/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients. 53
SAF-2 Figure 5. The Time Course of Total Protein (g/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients. 54
SAF-2 Figure 6. The Time Course of Uric Acid (mg/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients. 55
SAF-2 Figure 7. The Time Course of Brian Natriuretic Peptide (pg/mL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients. 56
SAF-4 Figure 1. The Time Course of Amylase (U/L) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients. 57
SAF-4 Figure 2. The Time Course of Creatinine (mg/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients. 58
SAF-4 Figure 3. The Time Course of Creatinine Kinase (U/L) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients. 59
SAF-4 Figure 4. The Time Course of LDL Cholesterol (mg/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients 60
SAF-4 Figure 5. The Time Course of Total Protein (g/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients. 61
SAF-4 Figure 6. The Time Course of Uric Acid (mg/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients. 62

Reference ID: 2917049

1. EXECUTIVE SUMMARY

The sponsor submitted data for their clinical program comprised of 24 phase I trials (among them 9 drug-drug interaction studies), 4 phase II trials, and 9 phase III trials including an open-label extension trial of the pivotal trials (1218.40) to support Linagliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. There are 4 pivotal efficacy and safety placebo-controlled phase III trials over 24 weeks (1218.15, 1218.16, 1218.17, and 1218.18). Information on long-term efficacy and safety is derived from a double-blind active-controlled phase III study which compared linagliptin with glimepiride added to a metformin background over 104 weeks (1218.20) of which only the interim data available from the sponsor. There are two supporting efficacy trials that are double-blind, placebo-controlled phase III trials with a treatment duration of 18 weeks: Study 1218.35 compared linagliptin with placebo added to an SU background, whereas study 1218.50 was conducted in patients ineligible for treatment with metformin. The data of the 4 pivotal studies (1218.15, 1218.16, 1218.17, and 1218.18) and 3 supportive trials (1218.20, 1218.35, and 1218.50) were presented in the drug labeling and therefore selected for statistical review.

A list of abbreviation and definition of terms has been provided in the NDA and is attached in this document as Appendix I.

1.1 Conclusions and Recommendations

1.1.1 Efficacy Conclusions:

Based on collective evidence of the 7 studies analyzed, this reviewer concludes that the data of above studies submitted by the sponsor are supportive to the efficacy claim of lina 5 mg treatment on T2DM patients population in above studies.

The non-inferiority of linagliptin 5 mg treatment against the glimepiride in HbA1c improvement is supported by a non-inferiority margin 0.35% in the interim efficacy analysis after 52 weeks treatment. In fact, linagliptin 5 mg is statistically worse than glimepiride in HbA1c change from baseline at every time point measured up to 78 weeks as well as the FPG measurement at Week 52. On the safety side, the hypoglycemia incidence rate in the lina 5 mg treated patients is significantly smaller than that in the glimepiride treated patients. In addition, the weight loss in the lina 5 mg treated patients is significantly greater than that in the glimepiride treated patients.

1.1.2 Safety Conclusion:

There appear to be no major differences between the trends of time course on the selected safety endpoints by FDA medical officer in comparing lina 5 mg treated patients to placebo treated patients (SAF-2) as well as to glimepiride treated patients (SAF-4). The selected safety endpoints do not include the major adverse cardiovascular events (MACE) which were reviewed by statisticians in the Division of Biometrics 7.

Reference ID: 2917049

1.2 Brief Overview of Clinical Studies

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. The applicant submitted data of studies to support Linagliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The submission includes 24 phase I trials (among them 9 drug-drug interaction studies), 4 phase II trials, and 9 phase III trials including an open-label extension trial of the pivotal trials (1218.40). There are 4 pivotal efficacy and safety placebo-controlled phase III trials over 24 weeks (1218.15, 1218.16, 1218.17, and 1218.18). Information on long-term efficacy and safety is derived from a double-blind active-controlled phase III study which compared linagliptin with glimepiride added to a metformin background over 104 weeks (1218.20) of which only the 52 week interim data available from the sponsor as indicated in Table 3.1. Supportive evidence of efficacy was provided by two double-blind, placebo-controlled phase III trials with a treatment duration of 18 weeks: Study 1218.35 compared linagliptin with placebo added to an SU background, whereas study 1218.50 was conducted in patients ineligible for treatment with metformin. The phase 3 studies whose results are shown in the sponsor proposed label are marked in the shaded area of Table 1.2.1 and are selected for review in this document.

Table 3.1. Summary of Clinical Trials Designed to Assess Safety and Efficacy

Study	Design	Patient Population	Treatment Groups (N)	Duration of Treatment
1218.05	Double-bind placebo-controlled (also include an open-label Met arm)	drug-naïve	Lina 0.5 mg (58) Lina 2.5 mg (57) Lina 5 mg (55) PBO (67)	12 weeks
1218.06	Double-bind placebo-controlled, Met add-on (also include an open-label Glm arm)	Met failure	Lina 1 mg + Met (65) Lina 5 mg + Met (66) Lina 10 mg + Met (66) PBO + Met (71)	12 weeks
1218.15	Pivotal double-bind placebo-controlled	drug-naïve	Lina 5 mg + Pio 30 mg (259) PBO + Pio 30 mg (130)	24 weeks
1218.16	Pivotal double-bind placebo-controlled	drug-naïve	Lina 5 mg (336) PBO (167)	24 weeks
1218.17	Pivotal double-bind placebo-controlled	Met failures	Lina 5 mg + Met (523) PBO + Met (177)	24 weeks
1218.18	Pivotal double-bind placebo-controlled	Met + SU failures	Lina 5 mg + Met + SU (792) PBO + Met + SU (263)	24 weeks
1218.20	Double-bind active-controlled	Met failures	Lina 5 mg + Met (778) Glm + Met (781)	52 weeks*
1218.23	Double-bind placebo- and active-controlled + safety extension	drug-naïve other than glitazones	Lina 5 mg (159) Lina 10 mg (160) PBO (80) Vog (162)	12 weeks (vs. PBO) 26 weeks (vs. Vog) 52 weeks (safety)
1218.35	Double-bind placebo-controlled	SU failure	Lina 5 mg + SU (161) PBO + SU (84)	18 weeks
1218.40	Open-label long-term extension	Type 2 diabetics^	Lina 5 mg (2121)	78 weeks ongoing
1218.50	Double-bind placebo-controlled + extension	Met inapproporiate	Lina 5 mg (151) PBO (76)	18 weeks (vs. PBO) 52 weeks (safety)

Reference ID: 2917049

Lina = linagliptin, PBO = placebo, Pio = pioglitazone, Met = metformin (≥1500 mg/day or maximum tolerated dose), SU = sulfonylurea (maximum tolerated), Vog = voglibose (0.6 mg/day), Glm= Glimepiride (1 to 4 mg/day)
* 104 weeks. On going. Data are available in interim analysis at 52 weeks
^ Patients with T2DM who had successfully completed the double-blind studies 1218.15, 1218.16, 1218.17 and 1218.18 irrespective of whether they had been treated with rescue medication.

1.3 Statistical Issues and Findings

The sponsor used LOCF to due with the missing values in their efficacy analyses.

2. INTRODUCTION

2.1 Overview

See section 1.2

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:	NDA201280/0000
Company	Boehringer Ingelheim
Drug	Linagliptin
CDER EDR link	\\CDSESUB1\EVSPROD\ NDA201280\0000
Letter date	7/6/2010

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 Evaluation of Efficacy

This section provides results from 7 phase 3 studies designed to establish the efficacy and safety of linagliptin in the monotherapy trials and add-on combination trials.

The primary endpoint for these studies is the change from baseline of HbA1c after pre-designed weeks of the treatments as specified in each trial.

Reference ID: 2917049

The key secondary endpoints (and other endpoints) include the change from baseline after pre-designed weeks of treatment in fasting plasma glucose (FPG), two-hour postprandial glucose (2hPPG) for Meal Tolerance Test (MTT), the occurrence of treat-to-target response (i.e. HbA1c on treatment <7.0% or <6.5%), weight, and hypoglycemia incidence.

The sponsor's primary analyses used an analysis of covariance (ANCOVA) method with the treatment and previous anti-diabetes therapy as fixed classification effects and baseline HbA1c as linear covariate on the full analysis set (FAS). The FAS 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 method (LOCF) was applied to the FAS. For studies 18 and 50, the fixed effects in the statistical model alter as specified in the two trials.

Unlike the sponsor's method for the primary analysis, this reviewer applied MMRM method with an additional fixed effect 'visit week' to the general model on the actually observed data, the OC population. This reviewer performed sensitivity analyses on per-protocol (PP), last observation carried forward (LOCF) populations, and the FAS-completers using MMRM method. All MMRM analyses examined the contrast at the last time point.

Note that patients would receive rescue therapy if the confirmed fasting plasma glucose value > 240 mg/dL and, in addition, a patient with glucose levels remain >240 mg/dl despite introduction of rescue therapy should be discontinued from the trial. The LOCF population used for the sponsor's primary efficacy analysis as well as for this reviewer's sensitivity analysis did not contain data after rescue.

The analysis described above is performed for the change from baseline after the pre-designed weeks of treatment in FPG, 2hPPG, and weight as listed in the proposed label, in an exploratory way based on the FAS and OC populations.

3.1.1 Monotherapy Trials

There are two monotherapy trials, Studies 16 and 50, to test superiority hypotheses against placebo in drug naïve or previously treated type 2 diabetic patients with insufficient glycaemic control. The design features of the two studies are shown in Table 3.1.1.

Table 3.1.1. Randomized, double-blind monotherapy trials

Study	Design	Patient Population	Treatment Groups (N)	Duration of Treatment
1218.16	Pivotal double-bind placebo-controlled	drug-naïve	Lina 5 mg (336) PBO (167)	24 weeks
1218.50	Double-bind placebo-controlled + extension	Met inapproporiate	Lina 5 mg (151) PBO (76)	18 weeks (vs. PBO) 52 weeks (safety)

Patient disposition and baseline demographics for the two monotherapy trials are summarized in Table 3.1.2 and Table 3.1.3, respectively

Reference ID: 2917049

Table 3.1.2. Patient disposition for monotherapy trials

Study population	Placebo	Lina 5 mg
Randomized		
Study 16	167	336
Study 50	76	151
Per Protocol		
Study 16	152 (91%)	314 (93%)
Study 50	68 (89%)	136 (90%)
Completers		
Study 16	148 (89%)	312 (93%)
Study 50	60 (79%)	133 (88%)
Rescued		
Study 16	34 (20%)	34 (10%)
Study 50	13 (17%)	17 (11%)

Table 3.1.3. Baseline demographics for monotherapy trials

	Study 16		Study 50	
	Placebo n=167	Lina 5 mg n=336	Placebo n=76	Lina 5 mg n=151
Age (yr)				
Mean(SE)	54 (10)	56 (10)	57 (10)	56 (11)
Range	28-75	24-79	36-79	20-80
% ≥65 yr	16%	23%	29%	24%
Gender				
% males	47%	49%	43%	36%
Race				
% White	54%	54%	33%	30%
			67%	70%
Region				
Asia	50%	50%	26%	26%
Europe	50%	50%	36%	38%
N. Am*	-	-	24%	19%
S. Am^	-	-	14%	17%
PAD	43%	44%	50%	46%
METFIND				
GI side effect	-	-	93%	93%
Creatinine ↑	-	-	7%	7%

* Include New Zealand, Australia
^ Include Mexico
PAD: Previous antidiabetic medication used
METFIND: Reason ineligible for metformin

Reference ID: 2917049

Study 16

Design

Study 16 is a randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycaemic control.

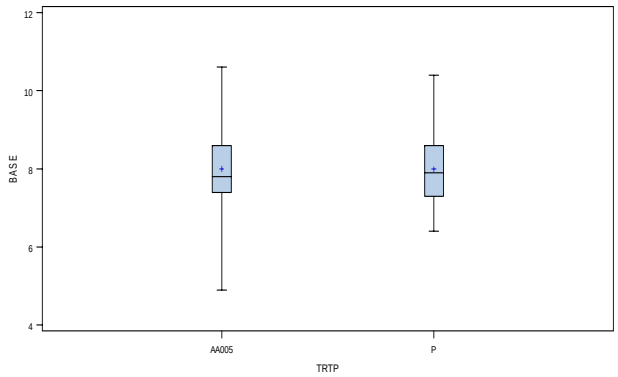
It was a multi-national, multi-centre trial with 66 trial sites in 11 countries (Croatia, India, Italy, Israel, Malaysia, Poland, Romania, Slovakia, Ukraine, Thailand, and Netherlands).

A total of 935 patients were enrolled into this study and 503 patients were randomized in a 1:2 ratio to either placebo (167 patients) or linagliptin (336 patients). Randomization was stratified by HbA1c at start of run-in (<8.5% versus ≥8.5%). The main reason for non-randomization was inclusion or exclusion criteria not met (38.2%).

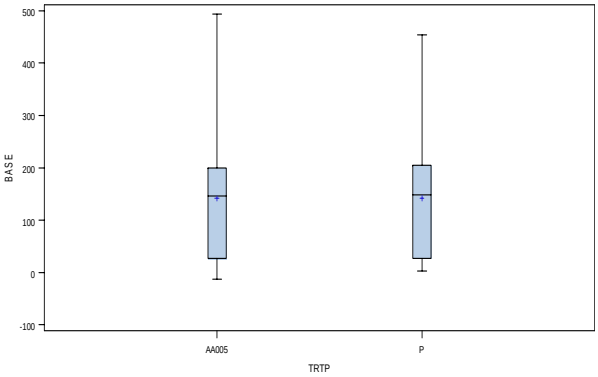
The baseline levels between linagliptin 5 mg and placebo for HbA1c and fasting plasma glucose, respectively, are compared in Figure 3.1.1. The base levels of HbA1c as well as fasting plasma glucose appear similar in both groups.

Figure 3.1.1. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo for Study 16 (OC population).

(a) Baseline HbA1c for study 16



(b) Baseline GLUC for study 16



Efficacy

The superiority of treatment with linagliptin 5 mg to placebo is tested for HbA1c change from baseline to week 24 at the level of α=0.05 (two-sided) on different analysis populations.

The treatment differences between linagliptin (n = 336) and placebo (n = 167), calculated as the adjusted mean change in HbA1c from baseline at Week 24, are summarized in Table 3.1.4 as the primary and sensitivity analyses. The results for the secondary endpoints, the fasting plasma glucose (FPG) and the 2-hour post-prandial glucose (PPG), compared with placebo are also listed in Table 3.1.4.

Reference ID: 2917049

Table 3.1.4. Glycemic Parameters in Placebo-Controlled Monotherapy Study 16 at Week 24

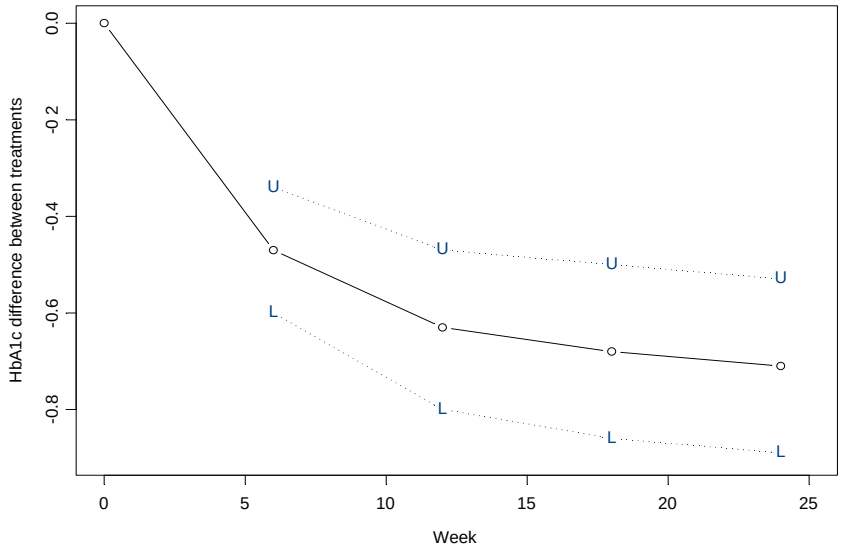
	Placebo N=167		Lina 5 mg N=336	
HbA1c (%)	n		n	
Baseline (SE)	167	7.99 (0.07)	336	8.00 (0.05)
Adjusted Mean Change from baseline (SE)				
OC	155	0.26 (0.08)	321	-0.45 (0.05)
LOCF	163	0.24 (0.07)	333	-0.45 (0.05)
sponsor's results of LOCF	163	0.25 (0.07)	333	-0.44 (0.05)
PP	145	0.24 (0.07)	308	-0.46 (0.05)
Completers	141	0.18 (0.07)	305	-0.47 (0.05)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-0.71 (-0.89, -0.53)
LOCF				-0.69 (-0.85, -0.52)
sponsor's results of LOCF				-0.69 (-0.85, -0.53)
PP				-0.72 (-0.87, -0.53)
Completers				-0.65 (-0.82, -0.47)
Patients (%) achieving HbA1c <7	25	15%	94	28%
sponsor's results	25	15%	94	28%
FPG (mg/dL)				
Baseline (SE)	159	168.7 (3.1)	326	164.7 (2.3)
Adjusted Mean Change from baseline (SE)				
OC	152	12.6 (3.0)	324	-8.5 (2.4)
LOCF	152	14.1 (3.0)	324	-8.5 (2.0)
sponsor's results of LOCF	149	14.8 (3.0)	318	-8.5 (2.0)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-21.1 (-28.2, -14.0)
LOCF				-22.6 (-29.7, -15.5)
sponsor's results of LOCF				-23.3 (-30.4, -16.3)
2-hour PPG (mg/dL)				
Baseline (SE)	24	243.8 (17.0)	67	258.0 (9.8)
Adjusted Mean Change from baseline (SE)		24.4 (10.4)		-33.7 (6.2)
sponsor's results		24.9 (10.3)		-33.5 (6.2)
Difference from placebo, adjusted LS Mean (95% CI)				-58.1 (-82.1, -34.1)
sponsor's result				-58.4 (-82.3, -34.4)

The linagliptin treatment is statistically superior to the placebo treatment on HbA1c reduction after 24 weeks treatment.

The time course of the completer's HbA1c difference between linagliptin 5 mg and placebo from their baseline is shown in Figure 3.1.2. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively.

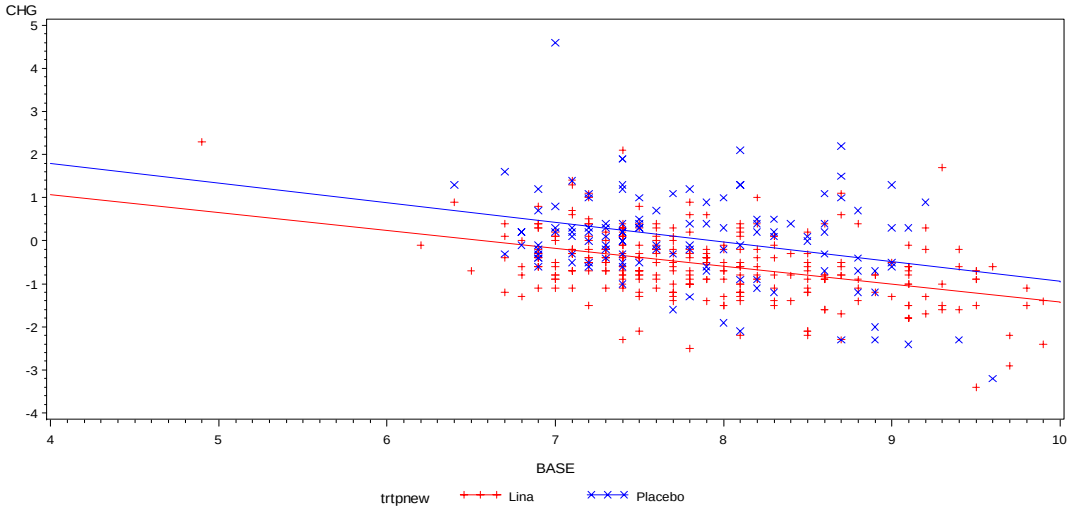
Reference ID: 2917049

Figure 3.1.2. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 16.



This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline as shown in Figure 3.1.3. The treatment-baseline interaction is not significant at alpha 0.10 level (p-value=0.71) using HbA1c baseline cutoff 8.5% to define baseline HbA1c strata used in the analysis.

Figure 3.1.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 16 at Week 24.



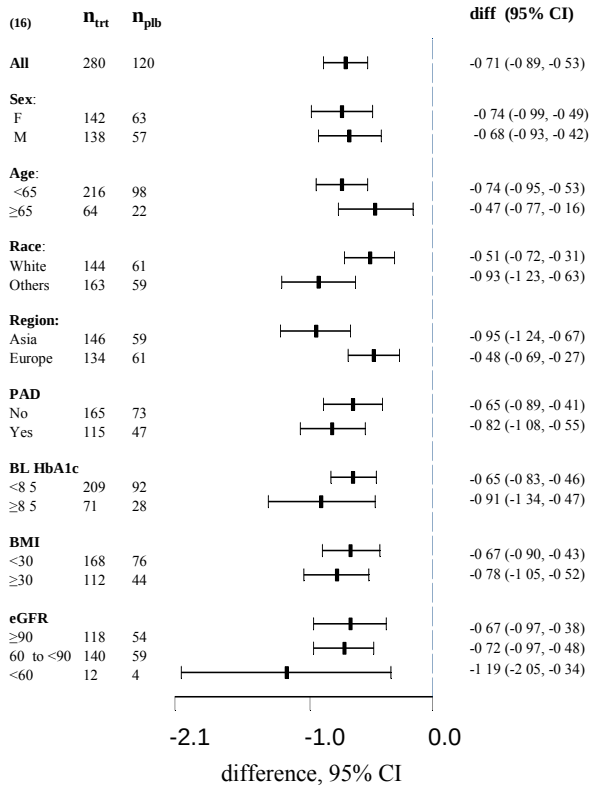
Regression equation: CHG(trtpnew:Lina 5 mg) = 2.73 - 0.41*BASE.
Regression equation: CHG(trtpnew:Placebo) = 3.63 - 0.46*BASE.

Reference ID: 2917049

Subgroup Analysis

This reviewer performed subgroup analyses on the primary endpoint HbA1c change between sex, age (<65 years, ≥ 65 years), race (white, others) as shown in the forest plot Figure 3.1.4. The other subgroup analyses are also explored, including regions, previous anti-diabetes therapy (PAD: Yes, No), HbA1c baseline level (BL HbA1c: <8.5%, ≥8.5%), BMI (<30, ≥30), and eGFR levels (≥ 90, 60 to <90, <60) as seen in Figure 3.1.4 as well.

Figure 3.1.4. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 16 by Subgroups.



Summary of Study 16: The analysis results support the superiority of linagliptin 5 mg treatment against the placebo in HbA1c improvement at every time measured up to 24 weeks. The superiority is supported by sensitivity analyses and glycemic measurements of FPG and 2-hour PPG.

Study 50

Design

Study 50 is a randomized, double-blind, placebo-controlled, parallel group efficacy and safety study of linagliptin (BI 1356) (5 mg), administered orally once daily for 18 weeks followed by a 34 week double-blind extension period (placebo patients switched to glimepiride) in type 2

Reference ID: 2917049

diabetic patients with insufficient glycaemic control for whom metformin therapy is inappropriate (intolerability or contraindication)

It was a multi-centre trial with 53 trial sites in 7 countries (Canada, Mexico, Philippines, Romania, Russia, Ukraine and USA)

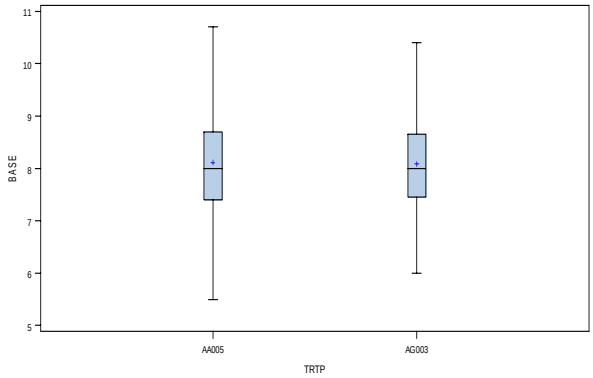
The primary analysis in part 1 (18 week treatment) is to test superiority hypothesis versus placebo using MMRM with treatment, visit week, and stratification variables (prior antidiabetic drugs and reason for ineligibility for treatment with metformin) as fixed effects and baseline HbA1c as covariate for HbA1c change from baseline after 18 weeks treatment.

A total of 571 patients were enrolled into this study and 227 patients were randomized in a 1:2 ratio to either placebo (76 patients) or linagliptin (151 patients). The main reason for non-randomization was inclusion or exclusion criteria not met (53.1% of enrolled patients). Randomization was stratified by HbA1c at Visit 2 (<8.5% versus ≥8.5%), the previous use of antidiabetes drugs (none, monotherapy) and reason for metformin ineligibility (gastrointestinal side effects, high creatinine levels).

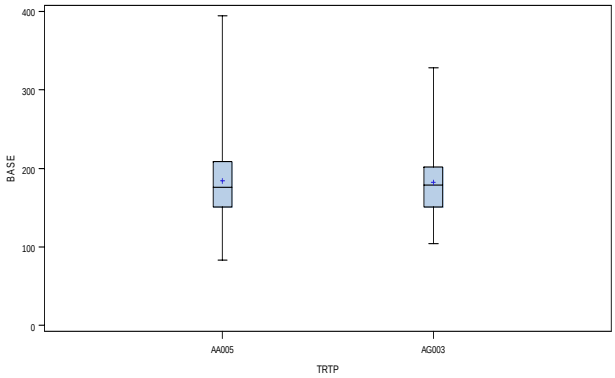
The baseline levels between linagliptin 5 mg and placebo for HbA1c and fasting plasma glucose, respectively, are compared in Figure 3.1.5. The base levels of HbA1c as well as fasting plasma glucose appear similar in both groups.

Figure 3.1.5. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo for Study 50 (OC population).

Baseline HbA1c study 50



Baseline GLUC study 50



Efficacy

The superiority of treatment with linagliptin 5 mg to placebo is tested for HbA1c change from baseline after 18 weeks treatment (the primary time point) at the level of α=0.05 (two-sided) on different analysis populations.

Reference ID: 2917049

This study was planned for one year and data were available for analysis after 18 weeks of treatment. The sponsor claimed that "No statistical adjustment due to multiple testing is required because at the time of the interim analysis all data for the primary endpoint will have been generated and data collected thereafter will not alter the primary outcome of the study. Therefore no multiple testing of the primary endpoint occurs which could inflate the risk of the type 1 error." This reviewer agrees with this.

The treatment difference between linagliptin (n=151) and placebo (n=76), calculated as the adjusted mean change in HbA1c from baseline at Week 18, adjusted for the stratification factors and baseline HbA1c, are summarized in Table 3.1.5 as the primary and sensitivity analyses. The results for the secondary endpoint, the fasting plasma glucose (FPG), compared with placebo are also listed in Table 3.1.5.

Table 3.1.5. Glycemic Parameters in Placebo-Controlled Monotherapy Study 50 at Week 18

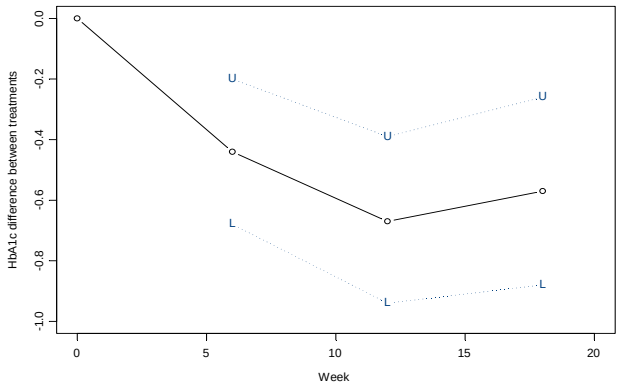
	Placebo N=76		Lina 5 mg N=151	
HbA1c (%)	n		n	
Baseline (SE)	76	8.09 (0.10)	151	8.12 (0.08)
Adjusted Mean Change from baseline (SE)				
OC	67	0.25 (0.13)	140	-0.33 (0.09)
LOCF	73	0.25 (0.11)	147	-0.30 (0.08)
sponsor's results of LOCF	73	0.14 (0.16)	147	-0.44 (0.14)
PP	62	0.22 (0.14)	129	-0.28 (0.09)
Completers	54	0.25 (0.13)	126	-0.33 (0.08)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-0.57 (-0.89, -0.26)
LOCF				-0.55 (-0.83, -0.27)
sponsor's results of LOCF				-0.57 (-0.86, -0.29)
PP				-0.50 (-0.82, -0.18)
Completers				-0.58 (-0.88, -0.28)
Patients (%) achieving HbA1c <7	11	15%	41	28%
sponsor's results	11	15%	41	28%
FPG (mg/dL)				
Baseline (SE)	73	180.5 (5.2)	147	183.3 (3.8)
Adjusted Mean Change from baseline (SE)				
OC	66	4.2 (4.3)	138	-14.6 (2.9)
LOCF	66	7.2 (4.4)	138	-13.6 (3.1)
sponsor's results of LOCF	66	7.2 (6.0)	138	-13.3 (5.2)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-18.8 (-29.0, -8.5)
LOCF				-20.8 (-31.3, -10.3)
sponsor's results of LOCF				-20.5 (-31.1, -9.9)

Reference ID: 2917049

The linagliptin treatment is statistically superior to the placebo treatment on HbA1c reduction after 18 weeks treatment.

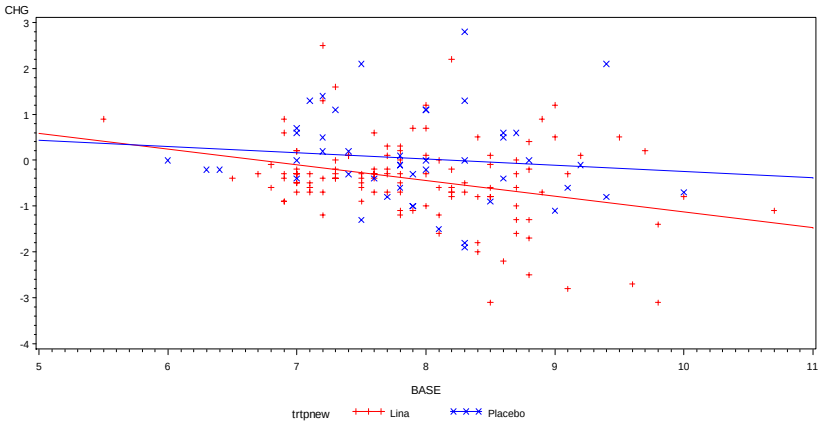
The time course of the completer's HbA1c difference between linagliptin 5 mg and placebo from their baseline is shown in Figure 3.1.6. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively.

Figure 3.1.6. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 50.



The relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline is shown in Figure 3.1.7. The treatment-baseline interaction is not significant at alpha 0.10 level (p-value=0.28) using HbA1c baseline cutoff 8.5% to define baseline HbA1c strata used in the analysis.

Figure 3.1.7. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 50 at Week 18.



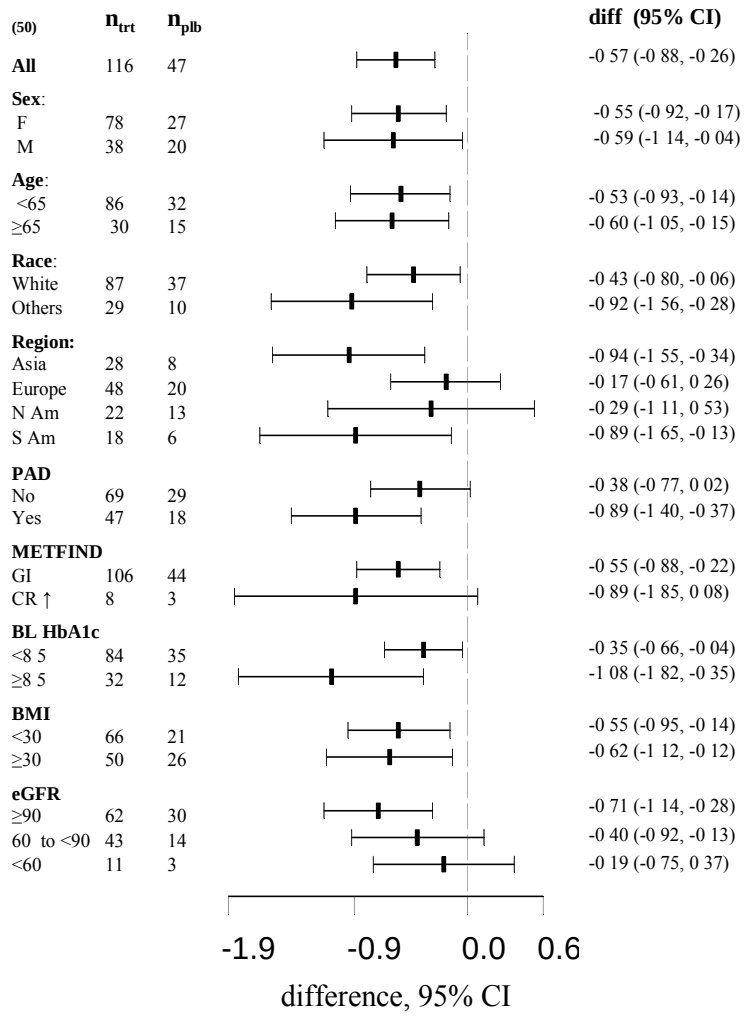
Regression equation: CHG(trtpnew:Lina 5 mg) = 2.30 - 0.34*BASE.
Regression equation: CHG(trtpnew:Placebo) = 1.11 - 0.14*BASE.

Reference ID: 2917049

Subgroup Analysis

This reviewer performed subgroup analyses on the primary endpoint HbA1c change between sex, age (<65 years, ≥ 65 years), race (white, others) as shown in the forest plot Figure 3.1.8. The other subgroup analyses are also explored, including regions, previous anti-diabetes therapy (PAD: Yes, No), reason for metformin ineligibility (METFIND, GI: gastrointestinal side effects, CR↑: high creatinine levels), HbA1c baseline level (BL HbA1c: <8.5%, ≥8.5%), BMI (<30, ≥30), and eGFR levels (≥ 90, 60 to <90, <60) as seen in Figure 3.1.8 as well.

Figure 3.1.8. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 50 by Subgroups.



Summary of Study 50: Above results support the superiority of linagliptin 5 mg treatment against the placebo in HbA1c improvement at every time measured up to 18 weeks. The superiority is supported by sensitivity analyses and FPG measurement.

Reference ID: 2917049

3.1.2 Add-On Trials

There are four add-on trials (Studies 17, 15, 35, and 18) to test superiority hypotheses against placebo in type 2 diabetic patients with insufficient glycaemic control despite the specified therapy as detailed in each study. One add-on trial, Study 20, tests non-inferiority hypothesis of linagliptin to glimepiride in combination with metformin in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy. The design features of these studies are shown in Table 3.1.6.

Table 3.1.6. Randomized, double-blind add-on trials

Study	Design	Patient Population	Treatment Groups (N)	Duration
1218.17	Pivotal double-bind placebo-controlled	Met failures	Lina 5 mg + Met (523) PBO + Met (177)	24 weeks
1218.15	Pivotal double-bind placebo-controlled	drug-naïve	Lina 5 mg + Pio 30 mg (259) PBO + Pio 30 mg (130)	24 weeks
1218.35	Double-bind placebo-controlled	SU failure	Lina 5 mg + SU (161) PBO + SU (84)	18 weeks
1218.18	Pivotal double-bind placebo-controlled	Met + SU failures	Lina 5 mg + Met + SU (792) PBO + Met + SU (263)	24 weeks
1218.20	Double-bind active-controlled	Met failures	Lina 5 mg + Met (778) Glm + Met (781)	52 weeks*

Patient disposition and baseline demographics for the 5 add-on trials are summarized in Table 3.1.7 and Table 3.1.8, respectively

Table 3.1.7. Patient disposition for add-on trials

	Placebo/comparator	Lina 5 mg
Randomized		
Study 17 Met	177	523
Study 20 Met	781	778
Study 15 Pio	130	258
Study 35 SU	84	161
Study 18 Met SU	263	792
Per Protocol		
Study 17 Met	156 (88%)	460 (88%)
Study 20 Met	433 (55%)	427 (55%)
Study 15 Pio	123 (95%)	246 (95%)
Study 35 SU	79 (94%)	156 (97%)
Study 18 Met SU	246 (94%)	733 (93%)
Completers		
Study 15 Pio	106 (82%)	236 (91%)
Stusy 17 Met	156 (88%)	468 (89%)
Study 20 Met	615 (79%)	630 (81%)
Stusy 18 Met SU	236 (90%)	725 (92%)
Stusy 35 SU	77 (92%)	150 (93%)
Rescued		
Study 15 Pio	18 (14%)	20 (8%)
Stusy 17 Met	33 (19%)	40 (8%)
Study 20 Met	94 (12%)	125 (16%)
Stusy 18 Met SU	34 (13%)	43 (5%)
Stusy 35 SU	13 (15%)	12 (7%)

Reference ID: 2917049

Table 3.1.8. Baseline demographics for all randomized and treated patients in add-on trials

	Study 17 Met		Study 20 Met		Study 15 Pio		Study 35 SU		Study 18 Met SU	
	Plb n=177	Lina 5 mg n=523	Glm n=781	Lina 5 mg n=778	Plb n=130	Lina 5 mg n=258	Plb n=84	Lina 5 mg n=161	Plb, n=263	Lina 5 mg n=792
Age (yr)										
Mean(SE)	57 (11)	57 (10)	60 (9)	60 (9)	57 (10)	58 (10)	56 (10)	57 (10)	58 (10)	58 (10)
Range	21-79	26-78	28-80	29-80	32-79	25-79	31-79	27-77	26-79	23-79
% ≥65 yr	23%	22%	33%	32%	27%	25%	17%	25%	27%	27%
Gender										
% males	57%	53%	61%	59%	65%	59%	62%	47%	48%	47%
Race										
% White	79%	75%	84%	85%	75%	74%	40%	45%	44%	47%
Region										
Africa	-	-	4%	4%	-	-	-	-	-	-
Asia	37%	41%	11%	11%	25%	25%	50%	47%	53%	49%
Europe	29%	25%	75%	76%	75%	75%	21%	29%	17%	19%
N. Am*	20%	18%	10%	9%	-	-	19%	16%	8%	9%
S. Am^	14%	16%	-	-	-	-	10%	9%	22%	22%
PAD	100%	100%	30%	30%	49%	50%	100%	100%	100%	100%
Rescued	19%	8%	12%	16%	14%	8%	15%	7%	13%	5%

* Include New Zealand, Australia
^ Include Mexico
PAD Previous antidiabetic medication

Study 17

Design

Study 17 is a randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy.

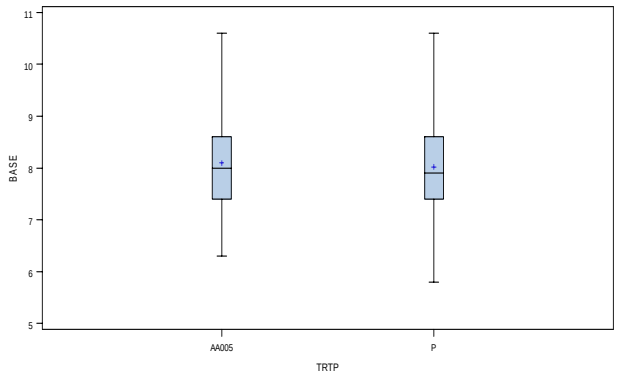
In this study, 1268 patients were enrolled in 82 centres of 10 countries (Czech Republic, Finland, Greece, India, Israel, Mexico, New Zealand, Russia, Sweden and USA) in Asia, Europe, North America and South America. A total of 701 patients were randomized in a 1:3 ratio to receive either placebo (177 patients) or linagliptin 5 mg (524 patients) in addition to ongoing background metformin therapy. Randomization was stratified by HbA1c at start of run-in (<8.5% versus ≥8.5%). About 45% of the enrolled patients were not randomized, mainly due to failure to meet the inclusion criteria regarding the range of HbA1c levels. A total of 700 patients (177 patients placebo; 523 patients linagliptin) were treated with randomized study medication.

The baseline levels between linagliptin 5 mg and placebo for HbA1c and fasting plasma glucose, respectively, are compared in Figure 3.1.9. The base levels of HbA1c as well as fasting plasma glucose appear similar in both groups.

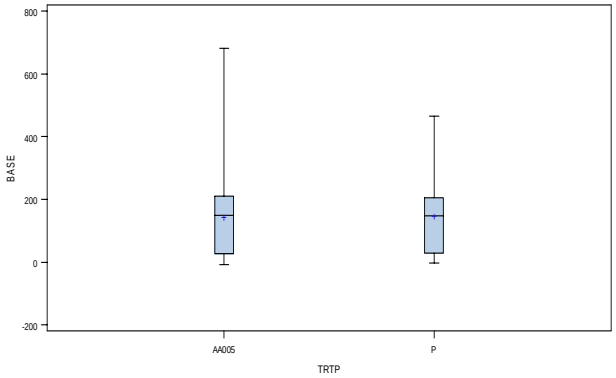
Reference ID: 2917049

Figure 3.1.9. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo for Study 17 (OC population).

Baseline HbA1c study 17



Baseline GLUC study 17



Efficacy

The superiority of treatment with linagliptin to placebo add-on to metformin is tested for HbA1c change from baseline to week 24 at the level of α=0.05 (two-sided).

The treatment differences between linagliptin (n = 523) and placebo (n = 177), calculated as the adjusted mean change in HbA1c from baseline at Week 24, are summarized in Table 3.1.9 in the primary and sensitivity analyses. The results for the secondary endpoints, the fasting plasma glucose (FPG) and the 2-hour post-prandial glucose (PPG), compared with placebo are also listed in Table 3.1.9.

Reference ID: 2917049

Table 3.1.9. Glycemic Parameters in Placebo-Controlled Add-on Study 17 at Week 24

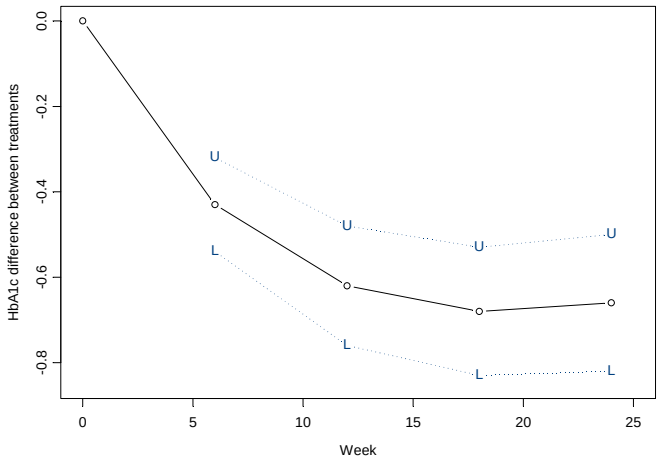
	Placebo N=177		Lina 5 mg N=523	
HbA1c (%)	n		n	
Baseline (SE)	177	8.02 (0.07)	523	8.10 (0.04)
Adjusted Mean Change from baseline (SE)				
OC	165	0.08 (0.07)	506	-0.58 (0.04)
LOCF	175	0.10 (0.06)	513	-0.55 (0.04)
sponsor's results of LOCF	175	0.15 (0.06)	513	-0.49 (0.04)
PP	148	0.07 (0.07)	455	-0.61 (0.04)
Completers	146	0.06 (0.07)	463	-0.59 (0.04)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-0.66 (-0.82, -0.50)
LOCF				-0.65 (-0.80, -0.50)
sponsor's results of LOCF				-0.64 (-0.78, -0.50)
PP				-0.68 (-0.84, -0.51)
Completers				-0.65 (-0.80, -0.49)
Patients (%) achieving HbA1c <7	20	11%	145	28%
sponsor's results	20	11%	145	28%
FPG (mg/dL)				
Baseline (SE)	172	166.4 (3.2)	503	169.6 (1.9)
Adjusted Mean Change from baseline (SE)				
OC	159	6.1 (2.7)	496	-12.6 (1.5)
LOCF	159	8.9 (2.8)	496	-12.1 (1.6)
sponsor's results of LOCF	175	10.5 (2.8)	513	-10.7(1.7)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-18.7 (-24.8, -12.6)
LOCF				-20.9 (-27.1, -14.7)
sponsor's results of LOCF				-21.1 (-27.3, -15.0)
2-hour PPG (mg/dL)				
Baseline (SE)	21	274.5 (14.9)	78	269.9 (7.5)
Adjusted Mean Change from baseline (SE)		25.5 (12.6)		-40.1 (6.6)
sponsor's results		18.3 (12.9)		-48.9 (7.4)
Difference from placebo, adjusted LS Mean (95% CI)				-65.6 (-93.7, -37.5)
sponsor's result				-67.1 (-94.7, -39.6)

The linagliptin treatment is statistically superior to the placebo treatment on HbA1c reduction after 24 weeks treatment.

The time course of the completer's HbA1c difference between linagliptin 5 mg and placebo from their baseline is shown in Figure 3.1.10. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively.

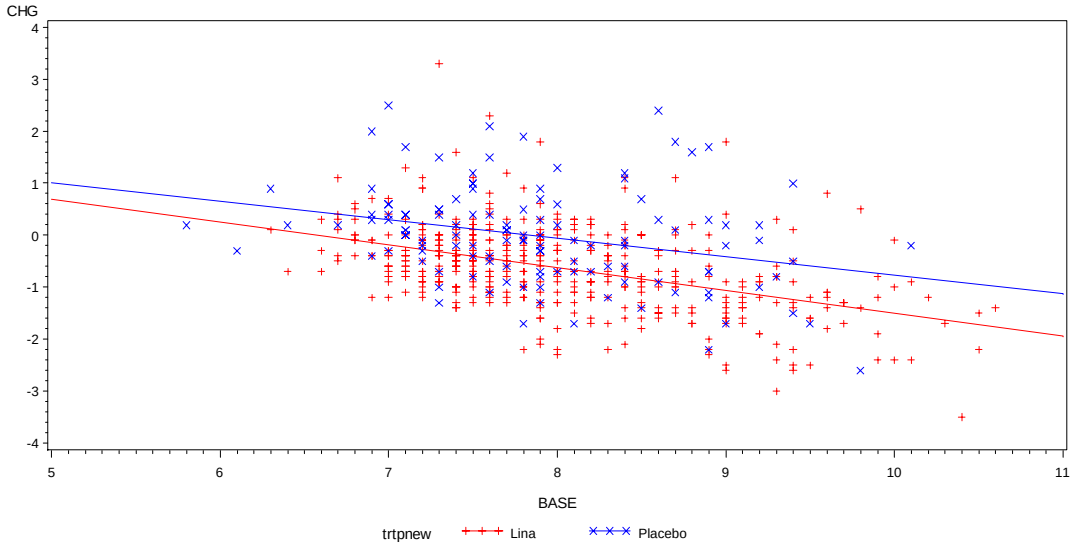
Reference ID: 2917049

Figure 3.1.10. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 17.



This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline as shown in Figure 3.1.11. The treatment-baseline interaction is not significant at alpha 0.10 level (p-value=0.38) using HbA1c baseline cutoff 8.5% to define baseline HbA1c strata used in the analysis.

Figure 3.1.11. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 17 at Week 24.



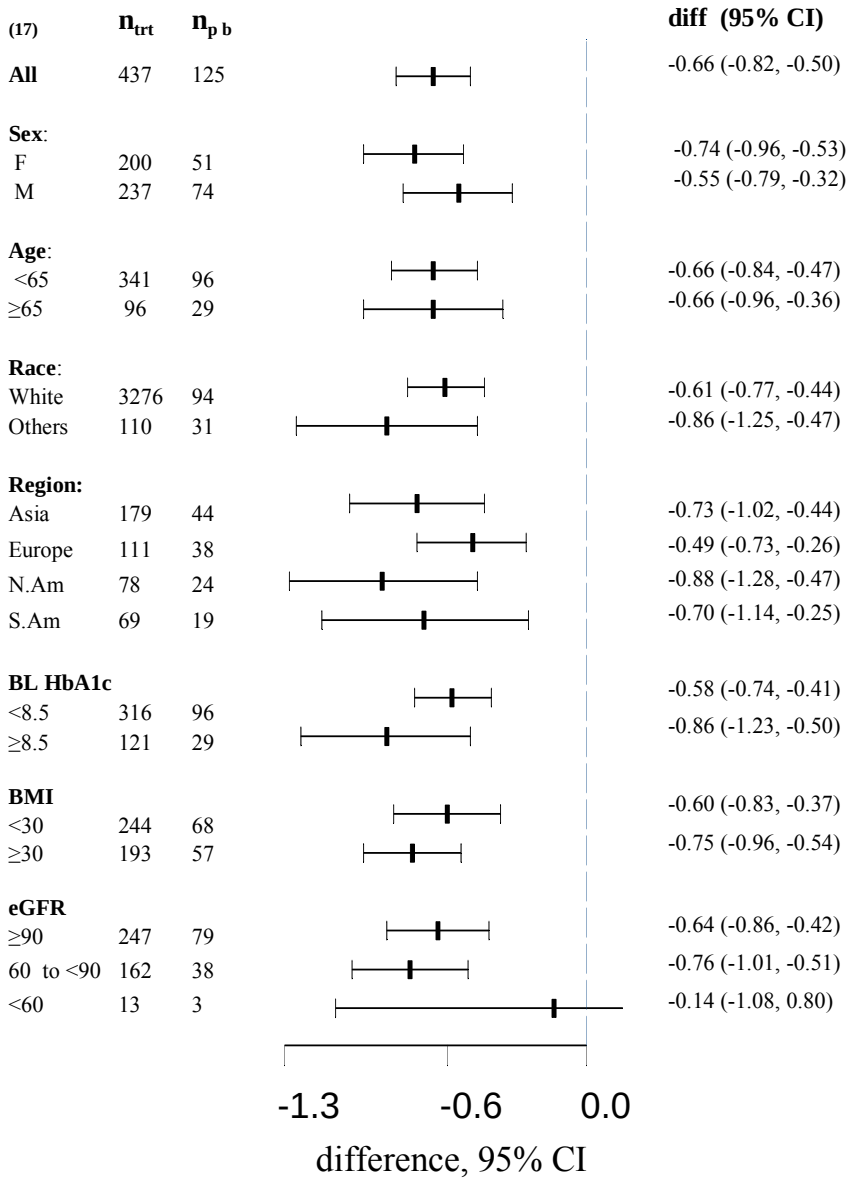
Regression equation: CHG(trtpnew:Lina 5 mg) = 2.90 - 0.44*BASE.
Regression equation: CHG(trtpnew:Placebo) = 2.77 - 0.35*BASE.

Reference ID: 2917049

Subgroup Analysis

This reviewer performed subgroup analyses on the primary endpoint HbA1c change between sex, age (<65 years, ≥ 65 years), race (white, others) as shown in the forest plot Figure 3.1.12. The other subgroup analyses are also explored, including regions, HbA1c baseline level (BL HbA1c: <8.5%, ≥8.5%), BMI (<30, ≥30), and eGFR levels (≥ 90, 60 to <90, <60) as seen in Figure 3.1.12 as well.

Figure 3.1.12. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 17 by Subgroups.



Reference ID: 2917049

Summary of Study 17: Above results support the superiority of linagliptin 5 mg treatment against the placebo as added to metformin in HbA1c improvement at every time measured up to 24 weeks. The superiority is supported by sensitivity analyses and glycemic measurements of FPG and 2-hour PPG.

Study 20:

Design

A randomized, double-blind, active-controlled parallel group efficacy and safety study of linagliptin (5 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy.

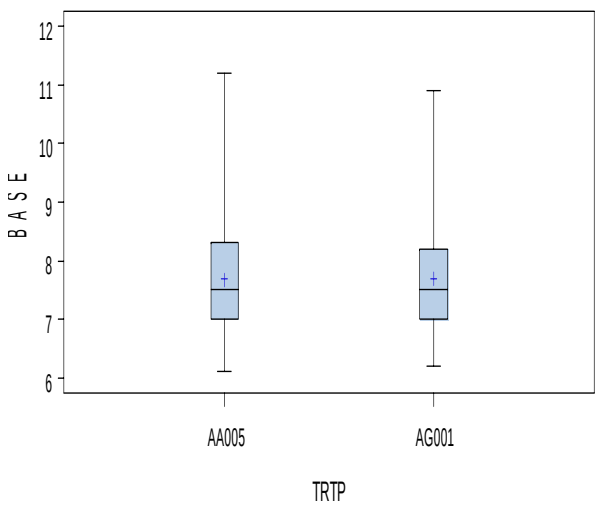
There were 209 trial sites in 16 countries (Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, UK, USA)

A total of 2300 patients were enrolled into this study, with 1560 patients being randomized in a 1:1 ratio to either linagliptin (779 patients) or glimepiride (781 patients). Randomization was stratified by HbA1c at start of run-in (<8.5% versus ≥8.5%). The main reason for non-randomization was inclusion criteria not met (21.9%). All but one of the randomized patients were treated (one patient in the linagliptin group was not treated).

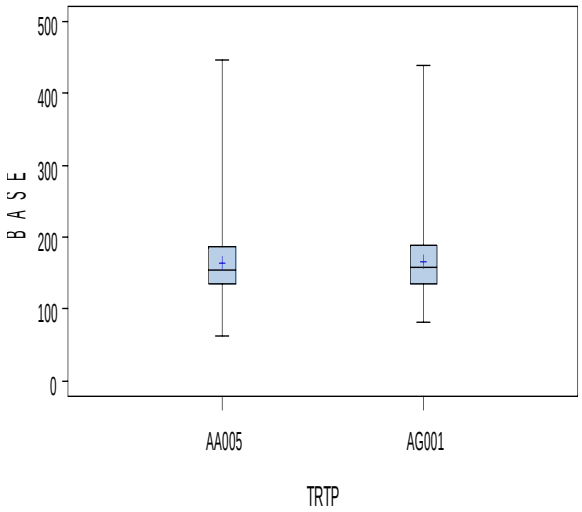
The baseline levels between linagliptin 5 mg and placebo for HbA1c and fasting plasma glucose, respectively, are compared in Figure 3.1.13. The base levels of HbA1c as well as fasting plasma glucose appear similar in both groups.

Figure 3.1.13. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Glimepiride for Study 20 (OC data of FAS population).

Baseline HbA1c study 20



Baseline GLUC study 20



Reference ID: 2917049

Efficacy

The primary analysis is an interim analysis after 52 weeks of treatment. The primary endpoint in this interim analysis was the change from baseline in HbA1c after 52 weeks of treatment. The 2 key secondary endpoints were the change in body weight from baseline to Week 52 and the occurrence of hypoglycaemic events up to 52 weeks of treatment (included in the safety results section). Other important secondary endpoints were the occurrence of treat-totarget response (i.e. HbA1c on treatment <7.0% or <6.5%), the change from baseline in fasting plasma glucose (FPG) at 52 weeks, and the change from baseline in 2 h post-prandial glucose (2h PPG) after 52 weeks of treatment.

As an adjustment for the multiple testing of endpoints after 52 weeks (for the interim analysis) and after 104 weeks (for the final analysis), the sponsor applied a Bonferroni correction. The total alpha (α) at 0.05 level (two-sided) was divided between the testing done at 52 weeks (α=0.025) and that done at 104 weeks (α=0.025).

The primary endpoint, HbA1c change from baseline to 52 weeks of treatment, was analyzed to test non-inferiority of linagliptin versus glimepiride at the level of α=0.025 (2-sided). The pre-set non-inferiority margin is 0.35%.

The treatment differences (Glim – Lina) between linagliptin (n = 778) and glimepiride (n = 781), calculated as the adjusted mean change in HbA1c from baseline at Week 52, are summarized in Table 3.1.10 in the primary and sensitivity analyses. The results for the secondary endpoint, the weight and fasting plasma glucose (FPG), compared with placebo are also listed in Table 3.1.10.

Reference ID: 2917049

Table 3.1.10. Glycemic Parameters in active-Controlled Add-on Study 20 at Week 52

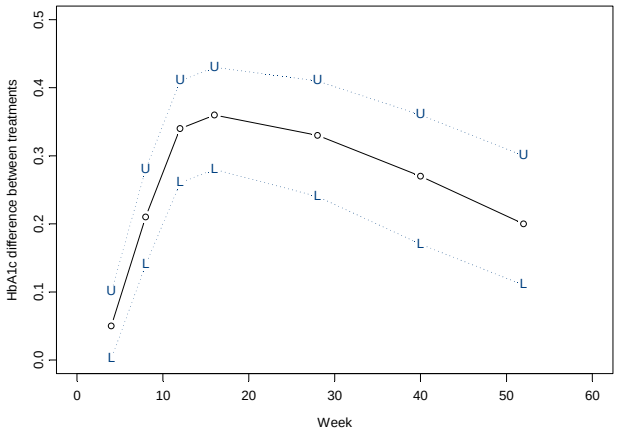
	Glimepiride N=781		Lina 5 mg N=778	
HbA1c (%)	n		n	
Baseline (SE)	781	7.68 (0.03)	778	7.70 (0.03)
Adjusted Mean Change from baseline (SE)				
OC	759	-0.64 (0.03)	763	-0.44 (0.03)
LOCF	761	-0.62 (0.03)	766	-0.39 (0.03)
sponsor's results of LOCF	761	-0.60 (0.03)	766	-0.38 (0.03)
PP	614	-0.75 (0.03)	628	-0.50 (0.03)
Completers	614	-0.65 (0.03)	628	-0.47 (0.03)
Difference from placebo, adjusted LS Mean (97.5% CI)				
OC				-0.20 (-0.30, -0.11)
LOCF				-0.22 (-0.32, -0.13)
sponsor's results of LOCF				-0.22 (-0.31, -0.13)
PP				-0.25 (-0.35, -0.14)
Completers				-0.19 (-0.28, -0.09)
Patients (%) achieving HbA1c <7	336	44%	303	40%
sponsor's results	340	45%	303	40%
FPG (mg/dL)				
Baseline (SE)	759	166.6 (1.5)	754	163.9 (1.6)
Adjusted Mean Change from baseline (SE)				
OC	734	-14.2 (1.3)	736	-9.3 (1.3)
LOCF	731	-16.2 (1.2)	736	-8.2 (1.2)
sponsor's results of LOCF	731	-16.2 (1.2)	736	-8.6 (1.2)
Difference from placebo, adjusted LS Mean (97.5% CI)				
OC				-5.0 (-8.9, -1.0)
LOCF				-8.0 (-11.8, -4.2)
sponsor's results of LOCF				-7.6 (-10.9, -4.3)
Weight (kg)				
Baseline (SE)	781	86.7 (0.6)	778	86.1 (0.6)
Adjusted Mean Change from baseline (SE)				
OC	730	1.5 (0.2)	736	-1.2 (0.2)
LOCF	730	1.4 (0.1)	736	-1.1 (0.1)
sponsor's results of LOCF	730	1.4 (0.1)	736	-1.1 (0.1)
Difference from placebo, adjusted LS Mean (97.5% CI)				
OC				2.7 (2.2, 3.2)
LOCF				2.5 (2.1, 2.9)
sponsor's results of LOCF				2.5 (2.1, 2.9)
Hypoglycemia incidence				
Incidence (%)	781	249 (31.9)	778	41 (5.3*)
sponsor's results		248 (31.8)		42 (5.4)

* p-value<0.0001 vs. glimepiride

Reference ID: 2917049

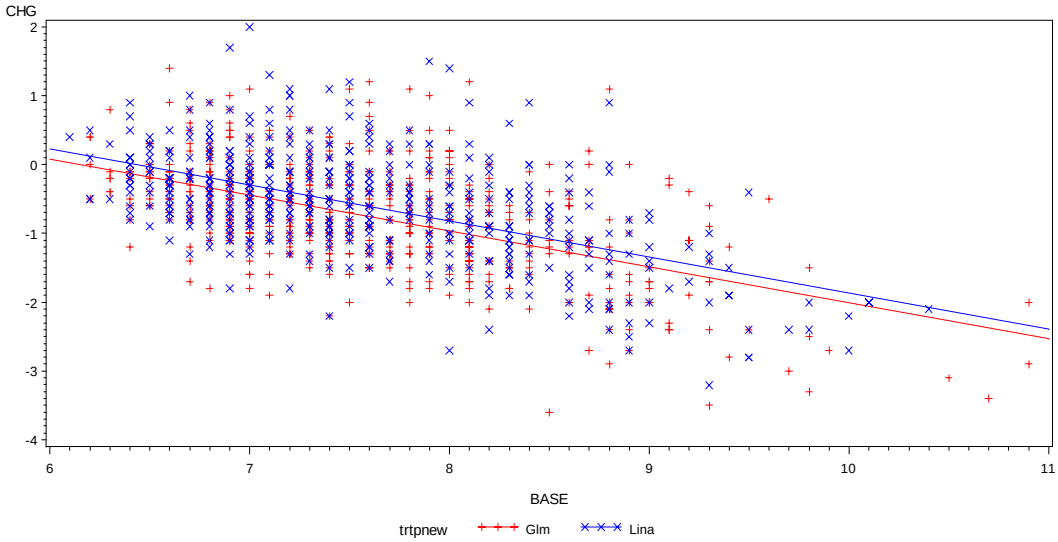
The time course of the completer's HbA1c difference between linagliptin 5 mg and glimepiride from their baseline is shown in Figure 3.1.14. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively.

Figure 3.1.14. The Time-course of HbA1c Difference between Linagliptin and Glimepiride Treatments in Study 20.



The relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline is shown in Figure 3.1.15. The treatment-baseline interaction is not significant at alpha 0.10 level (p-value=0.97) using HbA1c baseline cutoff 8.5% to define baseline HbA1c strata used in the analysis.

Figure 3.1.15. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and Glimepiride Treatments in Study 20 at Week 52.



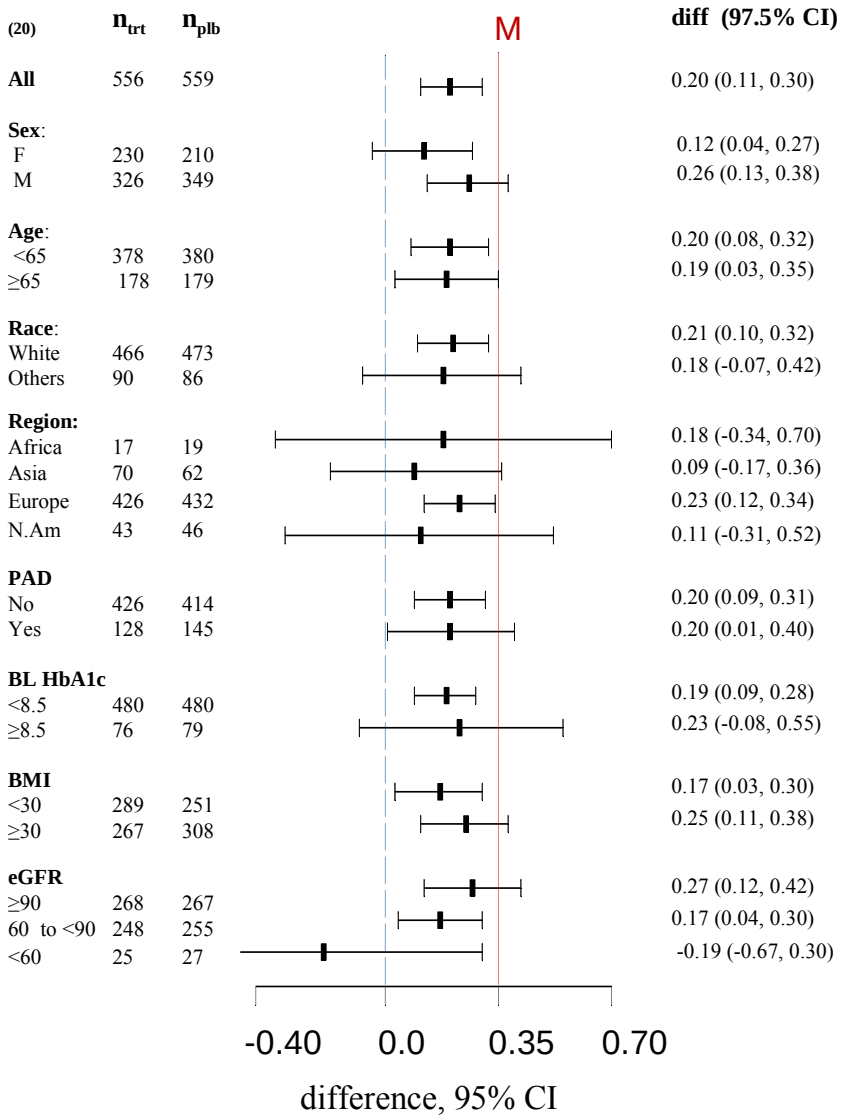
Regression equation: CHG(trtpnew:Lina 5 mg) = `3.360499 - 0.522367*BASE`
Regression equation: CHG(trtpnew:Glm) = `3.220266 - 0.523048*BASE`

Reference ID: 2917049

Subgroup Analysis

This reviewer performed subgroup analyses on the primary endpoint HbA1c change between sex, age (<65 years, ≥ 65 years), race (white, others) as shown in the forest plot Figure 3.1.16. The other subgroup analyses are also explored, including regions, previous anti-diabetes therapy (PAD: Yes, No), HbA1c baseline level (BL HbA1c: <8.5%, ≥8.5%), BMI (<30, ≥30), and eGFR levels (≥ 90, 60 to <90, <60) as seen in Figure 3.1.16 as well.

Figure 3.1.16. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and Glimepiride Treatments in Study 20 by Subgroups.



Reference ID: 2917049

Summary of Study 20: These results show that linagliptin 5 mg is statistically worse than glimepiride in HbA1c improvement at every time measured up to 78 weeks as well as the FPG measurement at Week 52. Linagliptin 5 mg is noninferior to glimepiride because the upper bound of the 95%CI excludes the pre-set HbA1c improvement NI margin of 0.35% on all analysis population except the PP with which the upper limit of the 97.5% confidence interval was 0.35% (On 2/25/2011, the sponsor claimed NI for PP after an error correction, but no updated data was submitted). The hypoglycemia incidence rate in the lina 5 mg treated patients is significantly smaller than that in the glimepiride treated patients. In addition, the weight loss in the lina 5 mg treated patients is significantly more than that in the glimepiride treated patients.

Study 15

Design

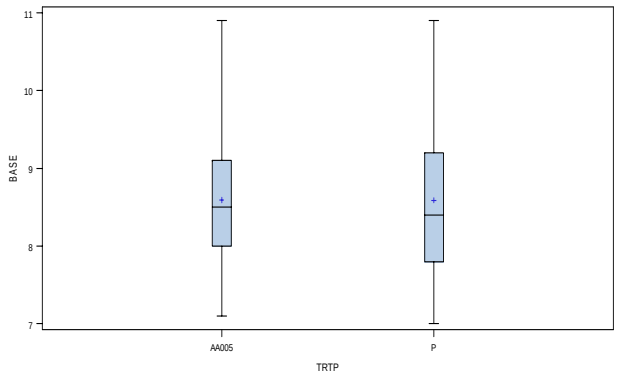
Study 15 is a randomized, double-blind, placebo controlled, parallel group, 24-week study to assess the efficacy and safety of linagliptin (5 mg) in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug-naïve or previously treated type 2 diabetic patients with insufficient glycaemic control.

In this study, 707 patients were enrolled in 43 centres in Europe and Asia (Austria, Greece, Hungary, Japan, Portugal, Romania, and Spain). A total of 389 patients were randomized in a 1:2 ratio to receive (once daily) either placebo plus pioglitazone 30 mg (pbo+pio), or linagliptin 5 mg plus pioglitazone 30 mg (lina+pio). Randomization was stratified by HbA1c at start of run-in (<8.5% versus ≥8.5%). About 45% (318 patients) of the enrolled patients were not randomized, mainly due to failure to meet the inclusion criteria regarding the range of HbA1c levels.

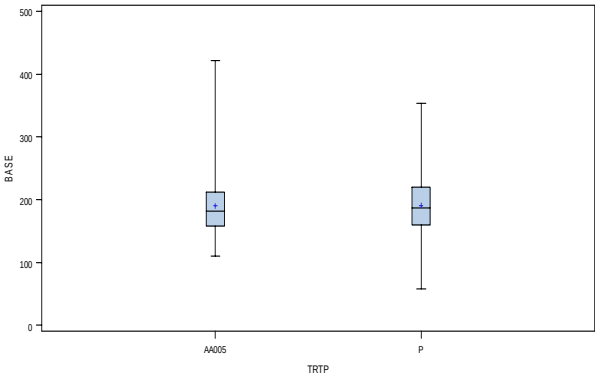
The baseline levels of linagliptin 5 mg and placebo in the pioglitazone add-on study for HbA1c and fasting plasma glucose, respectively, are compared in Figure 3.1.17. The base levels of HbA1c as well as fasting plasma glucose appear similar in both groups.

Figure 3.1.17. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo in the Pioglitazone Add-on Study 15 (OC data of FAS population).

(a) Baseline HbA1c study 15



(b) Baseline GLUC study 15



Reference ID: 2917049

Efficacy

The superiority of treatment with linagliptin 5 mg versus placebo in the pioglitazone add-on study is tested for HbA1c change from baseline to week 24 at the level of α=0.05 (two-sided).

The treatment differences between linagliptin (n = 259) and placebo (n = 130), calculated as the adjusted mean change in HbA1c from baseline at Week 24, are summarized in Table 3.1.11 in the primary and sensitivity analyses. The results for the secondary endpoint, the fasting plasma glucose (FPG), compared with placebo are also listed in Table 3.1.11.

Table 3.1.11. Glycemic Parameters in Placebo-Controlled Add-on to Pioglitazone Study 15 at Week 24

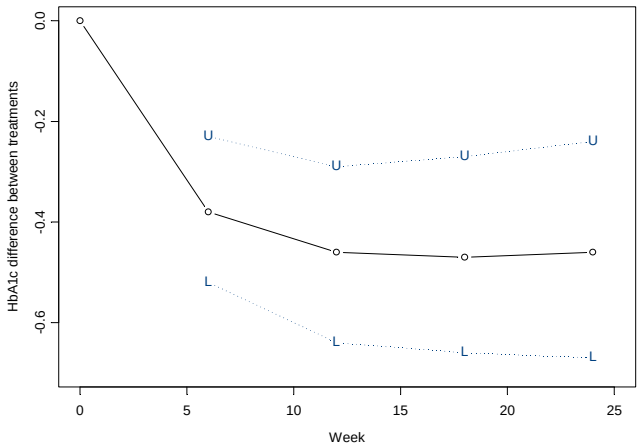
	Placebo N=130		Lina 5 mg N=529	
HbA1c (%)	n		n	
Baseline (SE)	130	8.59 (0.08)	258	8.60 (0.05)
Adjusted Mean Change from baseline (SE)				
OC	124	-0.85 (0.09)	249	-1.30 (0.06)
LOCF	129	-0.74 (0.09)	254	-1.26 (0.06)
sponsor's results of LOCF	128	-0.56 (0.09)	252	-1.06 (0.06)
PP	119	-0.88 (0.09)	241	-1.31 (0.06)
Completers	104	-0.87 (0.09)	231	-1.32 (0.06)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-0.46 (-0.67, -0.24)
LOCF				-0.51 (-0.72, -0.30)
sponsor's results of LOCF				-0.51 (-0.71, -0.30)
PP				-0.43 (-0.65, -0.21)
Completers				-0.45 (-0.68, -0.23)
Patients (%) achieving HbA1c <7	39	30%	108	43%
sponsor's results	39	30%	108	43%
FPG (mg/dL)				
Baseline (SE)	130	190.8 (3.8)	257	190.00 (2.7)
Adjusted Mean Change from baseline (SE)				
OC	123	-22.5 (2.9)	248	-35.4 (2.0)
LOCF	123	-21.7 (2.9)	248	-35.9 (2.0)
sponsor's results of LOCF	128	-18.4 (3.0)	252	-32.6 (2.2)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-12.9 (-19.9, -6.0)
LOCF				-14.2 (-21.1, -7.2)
sponsor's results of LOCF				-14.2 (-21.1, -7.3)

The linagliptin treatment is statistically superior to the placebo treatment on HbA1c reduction after 24 weeks treatment.

The time course of the completer's HbA1c difference between linagliptin 5 mg and placebo from their baseline is shown in Figure 3.1.18. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively.

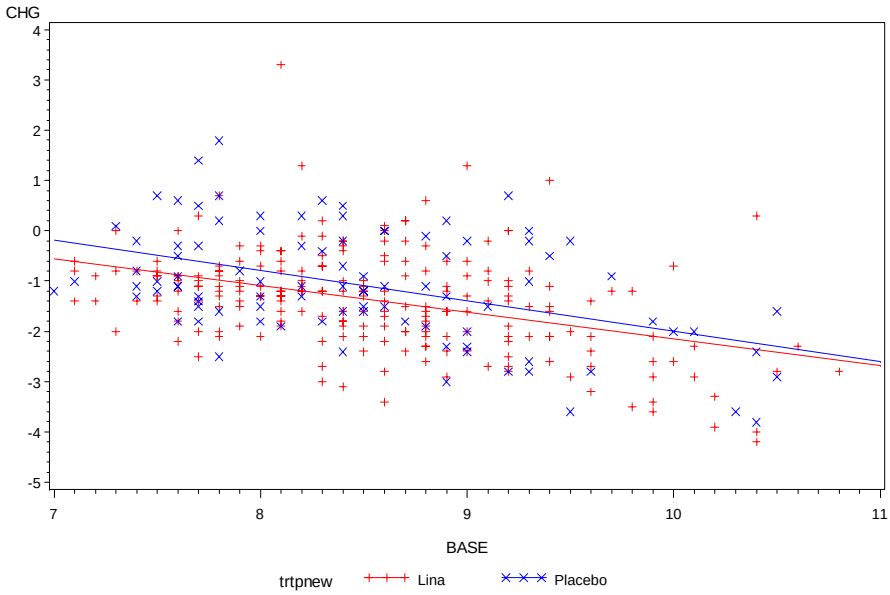
Reference ID: 2917049

Figure 3.1.18. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in the Pioglitazone Add-on Study 15 at Week 24.



This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline as shown in Figure 3.1.19. The treatment-baseline interaction is not significant at alpha 0.10 level (p-value=0.63) using HbA1c baseline cutoff 8.5% to define baseline HbA1c strata used in the analysis.

Figure 3.1.19. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 15 at Week 24.



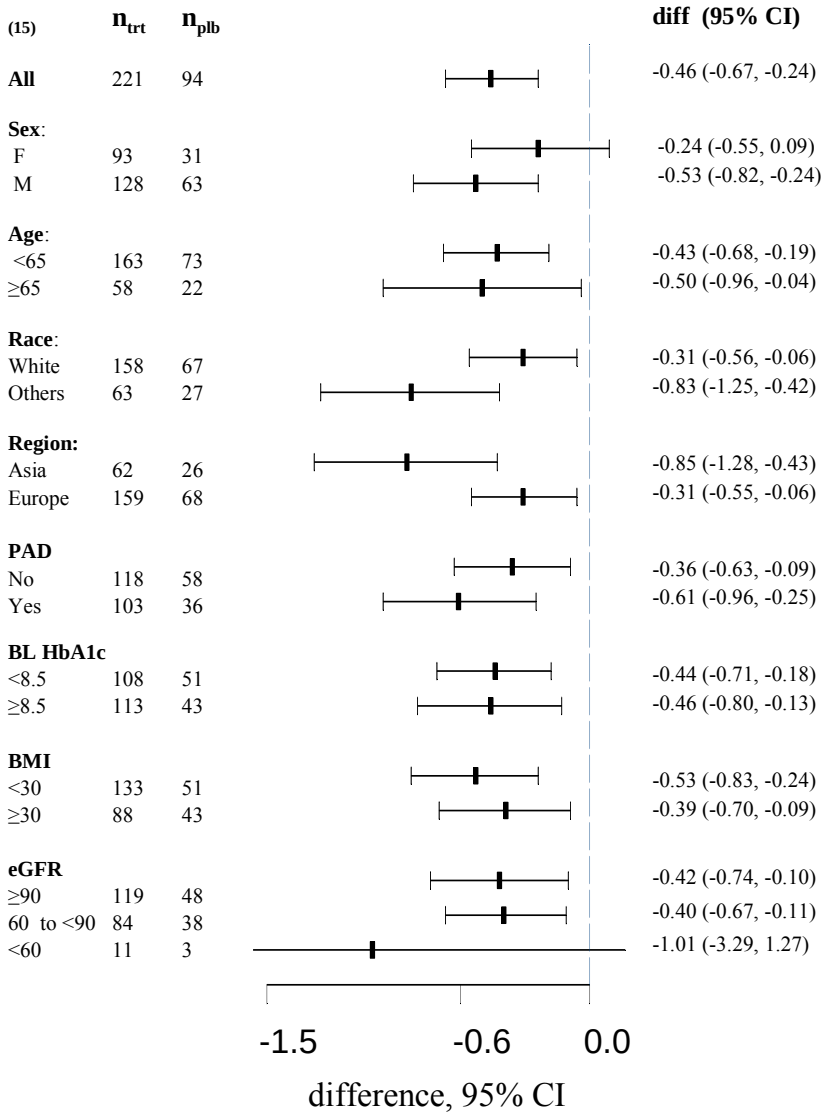
Regression equation: CHG(trtpnew:Lina 5 mg) = `3.145358 - 0.530119*BASE`
Regression equation: CHG(trtpnew:Placebo) = `4.027847 - 0.602358*BASE`

Reference ID: 2917049

Subgroup Analysis

This reviewer performed subgroup analyses on the primary endpoint HbA1c change between sex, age (<65 years, ≥ 65 years), race (white, others) as shown in the forest plot Figure 3.1.20. The other subgroup analyses are also explored, including regions, previous anti-diabetes therapy (PAD: Yes, No), HbA1c baseline level (BL HbA1c: <8.5%, ≥8.5%), BMI (<30, ≥30), and eGFR levels (≥ 90, 60 to <90, <60) as seen in Figure 3.1.20 as well.

Figure 3.1.20. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 15 by Subgroups.



It is noted that the upper bound of the HbA1c difference between linagliptin 5 mg and placebo from their baseline for females is not significant at the 0.05 level. As seen in Figure 3.1.21, the

Reference ID: 2917049

estimated HbA1c difference between treatments was increased at Week 24 as compared to that at Weeks 12 and 18, resulting an elevated upper 95% bound greater than 0 at Week 24. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively. The SAS output in Table 3.1.12 shows significant treatment by sex interaction effect in the model.

Figure 3.1.21. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 15.

15 female

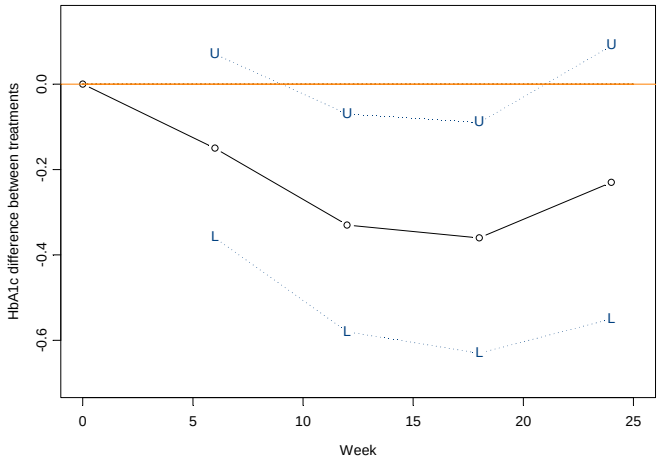


Table 3.1.12. SAS Output of the Type 3 Tests of Fixed Effects of the Model Containing Sex and Sex-Treatment Interaction Terms for Study 15 (OC data of FAS population).

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
BASE	1	365	22.64	<.0001
TRTP	1	365	12.66	0.0004
AVISITN	3	365	125.54	<.0001
SEX	1	365	6.48	0.0113
TRTP*SEX	1	365	3.57	0.0596

Summary of Study 15: The efficacy results of Study 15 support the overall superiority of linagliptin 5 mg treatment over the placebo as added to pioglitazone in HbA1c improvement at every time measured up to 24 weeks. The superiority is supported by sensitivity analyses and FPG measurement. Significant treatment by gender interaction is observed (p-value=0.06).

Study 35

Design

Reference ID: 2917049

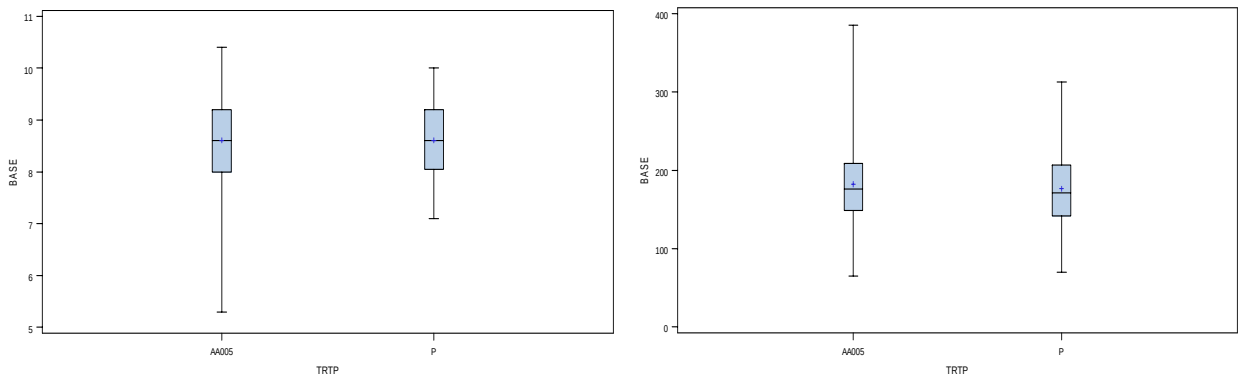
This is a randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 18 weeks in Type 2 diabetic patients with insufficient glycaemic control (HbA1c 7.0-10%) despite background therapy with a sulphonylurea drug.

A total of 471 patients were enrolled from 45 centers in Asia, Europe, North America and South America (8 countries: Argentina, Hungary, India, Japan, Poland, Russian, and USA). The randomization was stratified based on prior anti-diabetic drugs and the screening HbA1c value (<8.5% versus ≥8.5%) at the beginning of the placebo Run-in Period. A total of 280 patients entered the 2-week Placebo Run-in Period; 245 were randomized in a 1:2 ratio to placebo group (84 patients) and linagliptin 5 mg group (161 patients), respectively. All randomized patients were treated.

The baseline levels between linagliptin 5 mg and placebo as add-on to sulphonylurea for HbA1c and fasting plasma glucose, respectively, are compared in Figure 3.1.22. The base levels of HbA1c as well as fasting plasma glucose appear similar in both groups.

Figure 3.1.22. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo as Add-on to Sulphonylurea for Study 35 (OC data of FAS population).

(a) Baseline HbA1c study 35 **(b) Baseline GLUC study 35**



Efficacy

The superiority of treatment with linagliptin to placebo as add-on to sulphonylurea is tested for HbA1c change from baseline to week 18 at the level of α=0.05 (two-sided).

The treatment differences between linagliptin (n = 161) and placebo (n = 84), calculated as the adjusted mean change in HbA1c from baseline at Week 18, are summarized in Table 3.1.13 in the primary and sensitivity analyses. The results for the secondary endpoint, the fasting plasma glucose (FPG), compared with placebo are also listed in Table 3.1.13.

Table 3.1.13. Glycemic Parameters in Placebo-Controlled Sulphonylurea Add-on Study 35 at Week 18 (OC data of FAS population).

Reference ID: 2917049

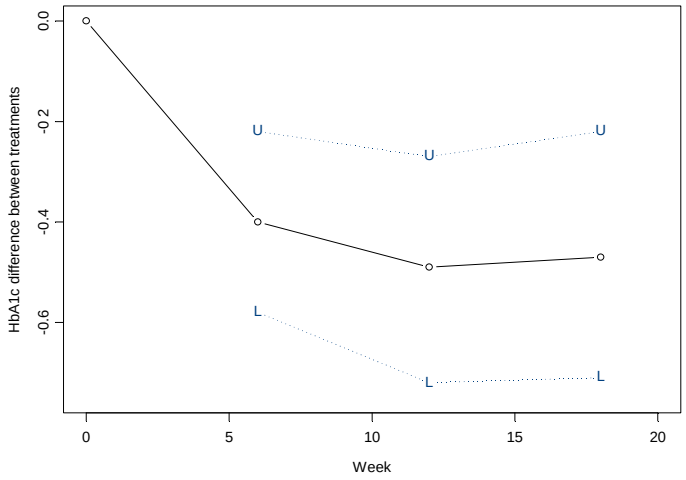
	Placebo N=84		Lina 5 mg N=161	
HbA1c (%)	n		n	
Baseline (SE)	84	8.61 (0.08)	161	8.61 (0.07)
Adjusted Mean Change from baseline (SE)				
OC	79	-0.13 (0.10)	155	-0.60 (0.07)
LOCF	82	-0.11 (0.09)	158	-0.58 (0.07)
sponsor's results of LOCF	82	-0.07 (0.10)	158	-0.54 (0.07)
PP	76	-0.16 (0.10)	153	-0.60 (0.07)
Completers	75	-0.13 (0.10)	147	-0.61 (0.07)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-0.47 (-0.71, -0.22)
LOCF				-0.46 (-0.69, -0.23)
sponsor's results of LOCF				-0.47 (-0.70, -0.24)
PP				-0.44 (-0.69, -0.20)
Completers				-0.47 (-0.72, -0.22)
Patients (%) achieving HbA1c <7	3	4%	24	15%
sponsor's results	3	4%	24	15%
FPG (mg/dL)				
Baseline (SE)	84	176.6 (5.5)	161	182.4 (4.1)
Adjusted Mean Change from baseline (SE)				
OC	78	-1.8 (4.7)	155	-8.0 (3.2)
LOCF	78	-1.4 (4.5)	155	-8.7 (3.2)
sponsor's results of LOCF	82	-1.8 (4.5)	158	-8.2 (3.3)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-6.2 (-17.4, 5.0)
LOCF				-7.3 (-18.1, 3.5)
sponsor's results of LOCF				-6.4 (-17.2, 4.3)

The linagliptin treatment is statistically superior to the placebo treatment on HbA1c reduction after 18 weeks treatment.

The time course of the completer's HbA1c difference between linagliptin 5 mg and placebo from their baseline is shown in Figure 3.1.23. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively.

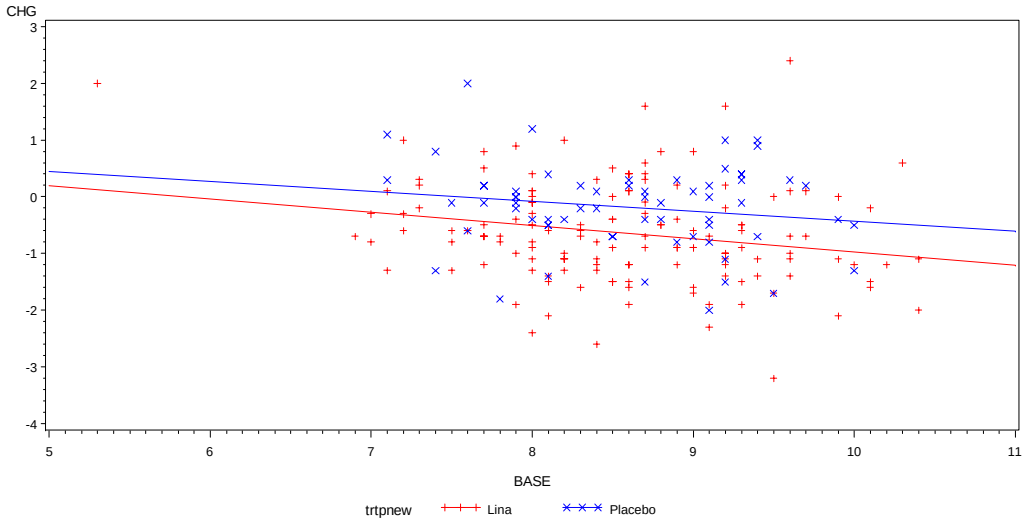
Reference ID: 2917049

Figure 3.1.23. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments as Add-on to Sulphonylurea of Study 35 (OC data of FAS population).



This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline as shown in Figure 3.1.24. The treatment-baseline interaction is not significant at alpha 0.10 level (p-value=0.99) using HbA1c baseline cutoff 8.5% to define baseline HbA1c strata used in the analysis.

Figure 3.1.24. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 35 at Week 18.



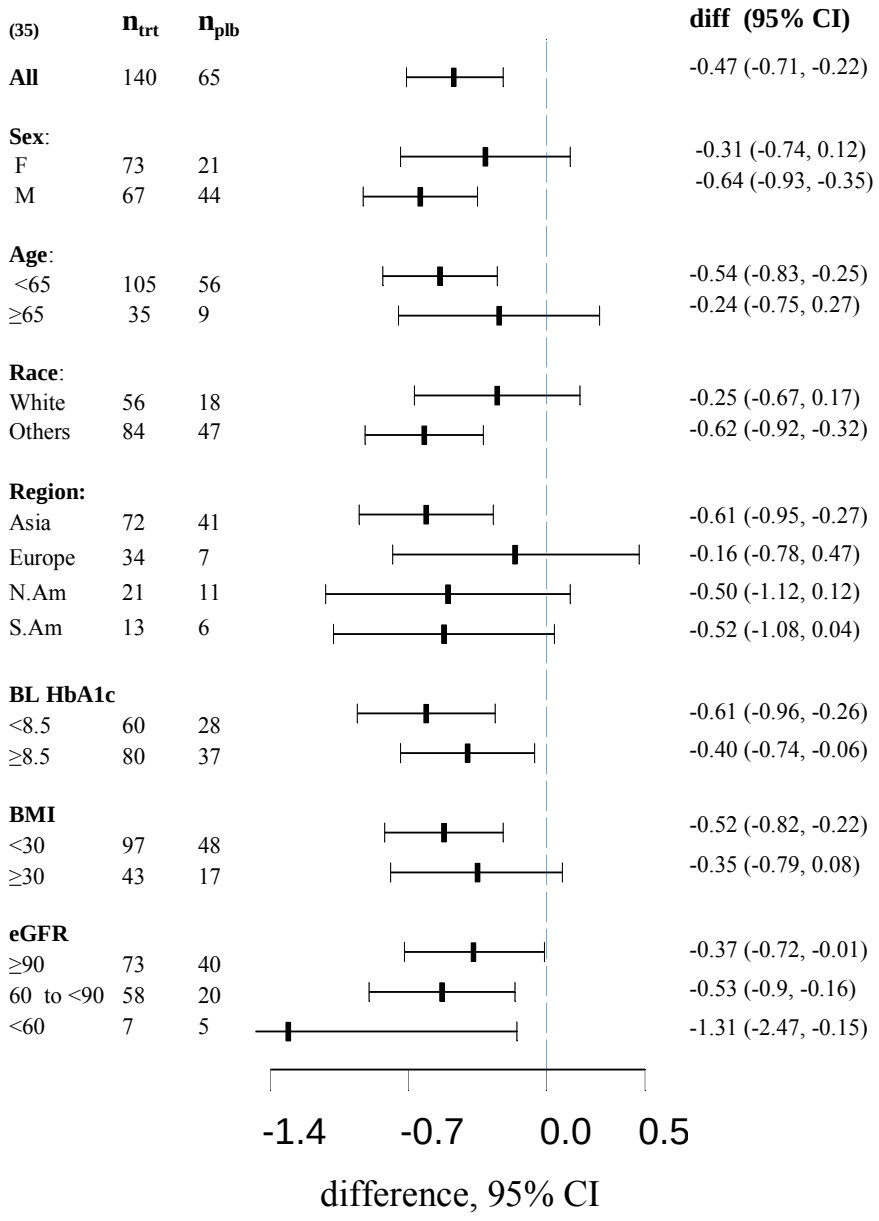
Regression equation: CHG(trtpnew:Lina 5 mg) = 1.36 - 0.23*BASE.
Regression equation: CHG(trtpnew:Placebo) = 1.33 - 0.18*BASE.

Reference ID: 2917049

Subgroup Analysis

This reviewer performed subgroup analyses on the primary endpoint HbA1c change between sex, age (<65 years, ≥ 65 years), race (white, others) as shown in the forest plot Figure 3.1.25. The other subgroup analyses are also explored, including regions, HbA1c baseline level (BL HbA1c: <8.5%, ≥8.5%), BMI (<30, ≥30), and eGFR levels (≥ 90, 60 to <90, <60) as seen in Figure 3.1.25 as well.

Figure 3.1.25. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments in Study 35 by Subgroups.



Reference ID: 2917049

It is noted that the upper bound of the HbA1c difference between linagliptin 5 mg and placebo from their baseline for females is not significant at the 0.05 level. As seen in Figure 3.1.26, the upper 95% bound of the estimated HbA1c differences between treatments were greater than 0 at Weeks 12 and 18. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively. However, the SAS output in Table 3.1.14 shows no significant treatment by sex interaction effect in the model.

Figure 3.1.26. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 35.

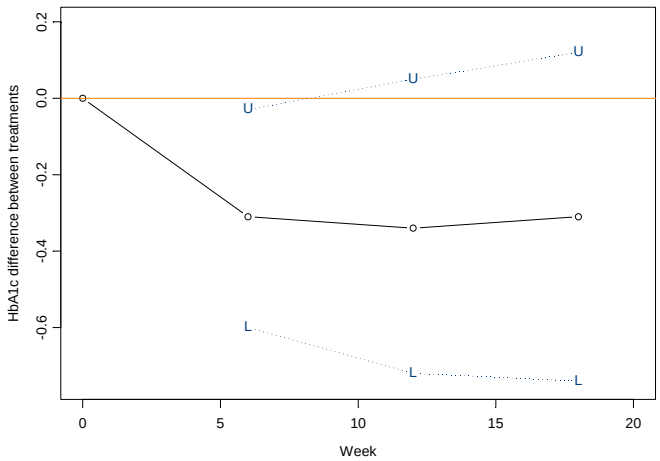


Table 3.1.14. SAS Output of the Type 3 Tests of Fixed Effects of the Model Containing Sex and Sex-Treatment Interaction Terms for Study 35 (OC data of FAS population).

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
BASE	1	229	5.56	0.0192
TRTP	1	229	21.31	<.0001
AVISITN	2	229	9.37	0.0001
SEX	1	229	2.76	0.0982
TRTP*SEX	1	229	1.46	0.2284

Summary of Study 35: Above results support the overall superiority of linagliptin 5 mg treatment against the placebo when added to sulphonylurea in HbA1c improvement at every time measured up to 24 weeks. The superiority is supported by sensitivity analyses and glycemic meatrurement of FPG.

Study 18

Reference ID: 2917049

Design

Study 18 is a randomized, double-blind placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg) administered orally once daily over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite a therapy of metformin in combination with a sulphonylurea.

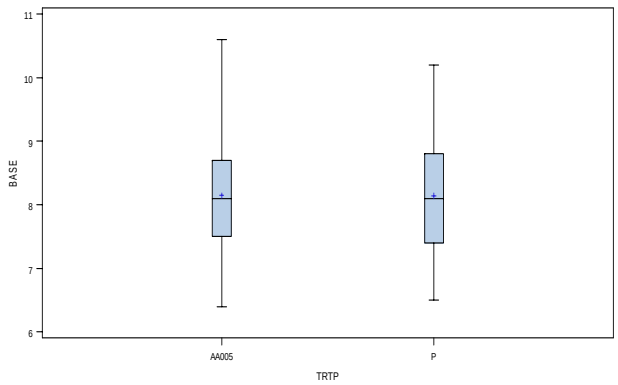
This was a multi-centre trial with 100 trial centers in 11 countries (Argentina, Belgium, Canada, China, Germany, Korea, Philippines, Russia, Taiwan, Turkey, and the United Kingdom).

A total of 1598 patients were enrolled; 1136 patients entered the 2-week placebo run-in period; 1058 were randomized in a 1:3 ratio to placebo group (265 patients) and linagliptin 5 mg group (793 patients), respectively, stratified by HbA1c (<8.5% versus ≥8.5%) as determined from the blood sample taken at the beginning of the placebo run-in period. Three of the randomized patients were not treated, and therefore 1055 patients were treated with either placebo (263 patients) or linagliptin (792 patients).

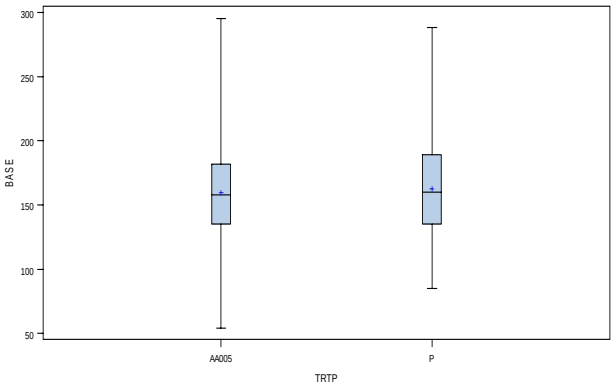
The baseline levels between linagliptin 5 mg and placebo for HbA1c and fasting plasma glucose, respectively, are compared in Figure 3.1.27. The base levels of HbA1c as well as fasting plasma glucose appear similar in both groups.

Figure 3.1.27. Baseline Levels of HbA1c (a) and Fasting Plasma Glucose (b) between Linagliptin 5 mg and Placebo as Add-on to Metformin and Sulphonylurea for Study 18 (OC data of FAS population).

(a) Baseline HbA1c study 18



(b) Baseline GLUC study 18



Efficacy

The superiority of treatment with linagliptin over placebo is tested for HbA1c change from baseline to week 24 at the level of α=0.05 (two-sided).

The treatment differences between linagliptin (n = 792) and placebo (n = 263), calculated as the adjusted mean change in HbA1c from baseline at Week 24, are summarized in Table 3.1.15 in the primary and sensitivity analyses. The results for the secondary endpoint, the fasting plasma glucose (FPG), compared with placebo are also listed in Table 3.1.15.

Reference ID: 2917049

Table 3.1.15. Glycemic Parameters in Placebo-Controlled Add-on Study 18 at Week 24

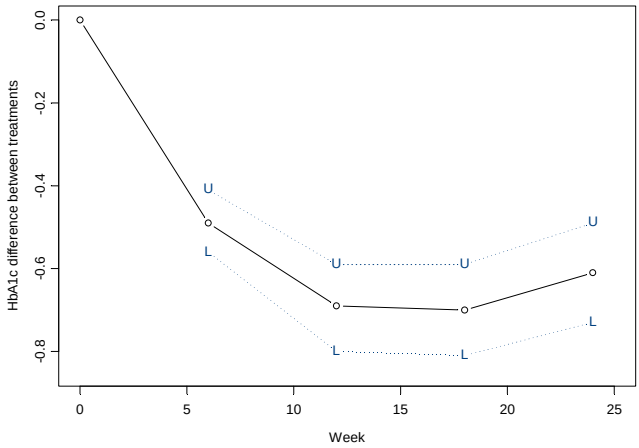
	Placebo N=263		Lina 5 mg N=792	
HbA1c (%)	n		n	
Baseline (SE)	263	8.14 (0.05)	792	8.15 (0.03)
Adjusted Mean Change from baseline (SE)				
OC	261	-0.11 (0.05)	774	-0.72 (0.03)
LOCF	262	-0.10 (0.05)	778	-0.72 (0.03)
sponsor's results of LOCF	262	-0.10 (0.05)	778	-0.72 (0.03)
PP	246	-0.13 (0.05)	732	-0.73 (0.03)
Completers	235	-0.14 (0.05)	721	-0.74 (0.03)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-0.61 (-0.73, -0.49)
LOCF				-0.62 (-0.73, -0.50)
sponsor's results of LOCF				-0.62 (-0.73, -0.50)
PP				-0.60 (-0.73, -0.48)
Completers				-0.60 (-0.72, -0.48)
Patients (%) achieving HbA1c <7	24	9%	242	31%
sponsor's results	24	9%	243	31%
FPG (mg/dL)				
Baseline (SE)	251	162.7 (2.3)	759	159.4 (1.3)
Adjusted Mean Change from baseline (SE)				
OC	252	7.3 (2.5)	757	-5.7 (1.4)
LOCF	252	7.9 (2.4)	757	-4.5 (1.4)
sponsor's results of LOCF	262	8.1 (2.4)	778	-4.6 (1.4)
Difference from placebo, adjusted LS Mean (95% CI)				
OC				-13.0 (-18.5, -7.4)
LOCF				-12.4 (-17.8, -7.0)
sponsor's results of LOCF				-12.7 (-18.1, -7.3)

The linagliptin treatment is statistically superior to the placebo treatment on HbA1c reduction after 24 weeks treatment.

The time course of the completer's HbA1c difference between linagliptin 5 mg and placebo as add-on to metformin and sulphonylurea from their baseline is shown in Figure 3.1.28. At each time point, the 95% confidence bounds are represented as the upper bound "U" and the lower bound "L", respectively.

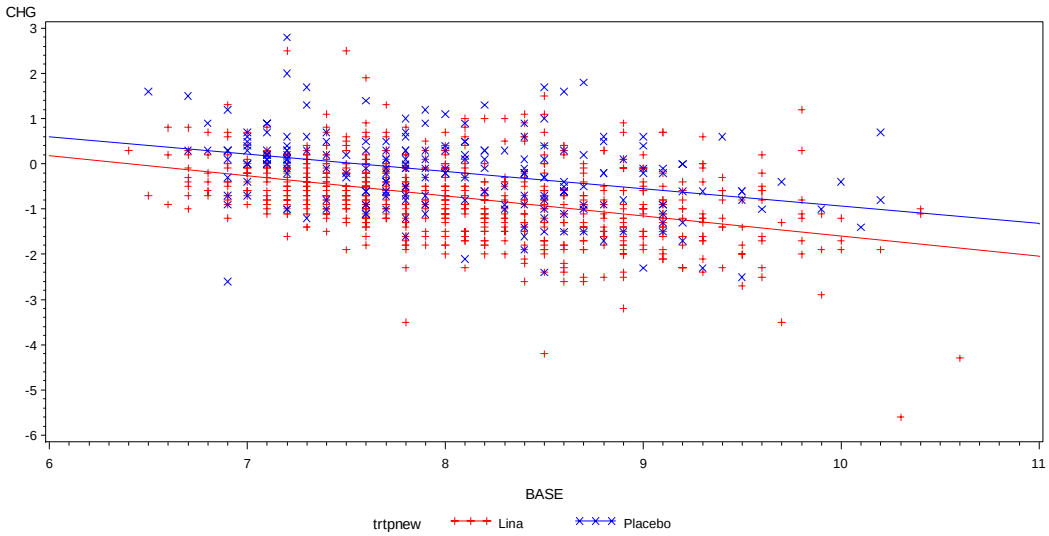
Reference ID: 2917049

Figure 3.1.28. The Time-course of HbA1c Difference between Linagliptin and placebo Treatments in Study 18.



This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline as shown in Figure 3.1.29. The treatment-baseline interaction is not significant at alpha 0.10 level (p-value=0.20) using HbA1c baseline cutoff 8.5% to define baseline HbA1c strata used in the analysis.

Figure 3.1.29. The Plot of HbA1c Changes from Baseline versus Baseline Levels between Linagliptin 5 mg and placebo Treatments in Study 18 at Week 24.



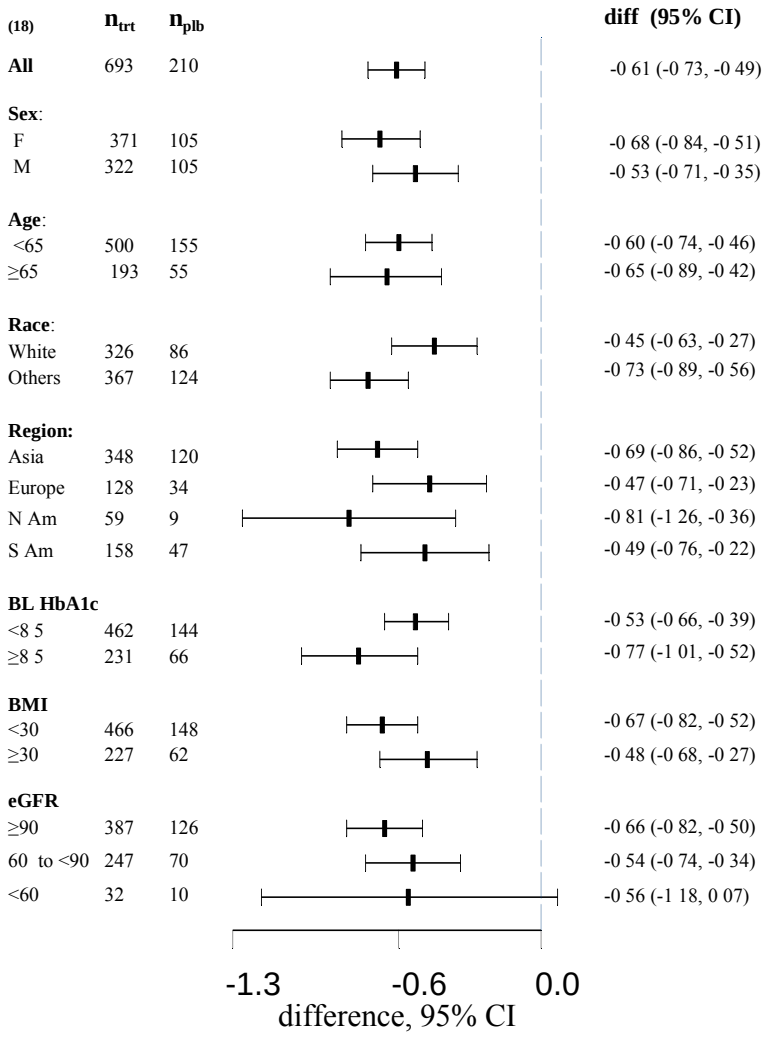
Regression equation: CHG(trtpnew:Lina 5 mg) = 2.86 - 0.45*BASE.
Regression equation: CHG(trtpnew:Placebo) = 2.89 - 0.38*BASE.

Reference ID: 2917049

Subgroup Analysis

This reviewer performed subgroup analyses on the primary endpoint HbA1c change between sex, age (<65 years, ≥ 65 years), race (white, others) as shown in the forest plot Figure 3.1.30. The other subgroup analyses are also explored, including regions, HbA1c baseline level (BL HbA1c: <8.5%, ≥8.5%), BMI (<30, ≥30), and eGFR levels (≥ 90, 60 to <90, <60) as seen in Figure 3.1.30 as well.

Figure 3.1.30. The Forest Plot of HbA1c Difference between Linagliptin 5 mg and placebo Treatments as Add-on to Metformin and Sulphonylurea in Study 18 by Subgroups.



Summary of Study 18: Above results support the superiority of linagliptin 5 mg treatment over placebo as added to metformin and sulphonylurea in HbA1c improvement at every time measured up to 24 weeks. The superiority is supported by sensitivity analyses and glycemic measurement of FPG.

Reference ID: 2917049

Summary of Efficacy of Add-on Studies: The efficacy results in the add-on studies (17, 15, 35, and 18) support the overall superiority of linagliptin 5 mg treatment over placebo in HbA1c improvement and in the planned glycemic measurements at the end of treatment. The overall efficacy results from Study 20 support the non-inferiority of linagliptin 5 mg to glimepiride.

3.2 Evaluation of Safety

This reviewer conducted safety analyses on safety endpoints identified by the FDA medical officer by comparing the trends of time course between the patients treated with linagliptin 5 mg and with placebo (SAF-2) as well with active comparator glimepiride (SAF-4). These safety endpoints include the laboratory measurements of amylase, creatinine, creatinine kinase, LDL cholesterol, protein, uric acid (urate), and brain natriuretic peptide. The data of brain natriuretic peptide value was available only in study 15. The information of the pooled datasets for SAF-2 and SAF-4 are shown in Table 3.2.1 and Table 3.2.2, respectively.

Table 3.2.1. Summary of SAF-2 Data Information

Study	Phase	Treatment duration	N, lina 5 mg	N, placebo
1218.2	I	12 days	9	12
1218.3	I	28 days	16	16
1218.5	II	12 weeks	55	67
1218.6	II	12 weeks	66	71
1218.15	III	24 weeks	259	130
1218.16	III	24 weeks	336	167
1218.17	III	24 weeks	524	177
1218.18	III	24 weeks	793	265
1218.23*	III	12 weeks	159	80
1218.35	III	18 weeks	161	84
1218.37	III	4 weeks	40	40
1218.50	III	18 weeks	151	76
All			2569	1185
Total			3754	

* Only patients in the double-blind treatment phase (the 1st stage) treated with lina 5 mg and placebo were included.

Table 3.2.2. Summary of SAF-4 Data Information

Study	Phase	Treatment duration	N, lina 5 mg	N, glimepiride
1218.20	III	≥52 weeks	779	781
Total			1559	

There were multiple laboratory measurements for each patient from screening visit to the last visit with sample collected. This reviewer plotted all measurements at each time point and fitted

Reference ID: 2917049

regression lines to the data, one for each treatment group. The regression lines provide a rough measure of whether the laboratory values are changing over time.

The plots of SAF-2 endpoints are shown in Appendix II SAF-2 Figures 1 to 7. From each plot, the trends over time of the two treatments look similar. There is also substantial variability of the laboratory values. Linagliptin patients had higher values for amylase and total serum protein than did placebo patients whereas linagliptin patients had lower values for creatinine, LDL, and brain natriuretic peptide than did placebo patients. The two treatments displayed similar trends over time for uric acid and creatinine kinase.

Summary of SAF-2 time courses: the overall time course of the selected safety endpoints appears to be similar between patients treated with lina 5 mg and placebo with large variability in the laboratory values.

The plots of SAF-4 endpoints are shown in Appendix III. SAF-4 Figures 1 to 6 show similar trends between linagliptin 5 mg and glimepirid treated patients for the safety endpoints. There is also substantial variability of the laboratory values. Linagliptin patients appear to have lower values for all selected endpoints except LDL than did placebo patients.

Summary of SAF-4 time courses: the overall time course of the selected safety endpoints appears to be similar between patients treated with lina 5 mg and glimepiride with large variability in the laboratory values.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

See 3.1.

Reference ID: 2917049

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Efficacy

Based on the results by the sponsor and this reviewer, the superiority of linagliptin 5 mg treatment against the placebo in HbA1c improvement is supported in

- the monotherapy studies
  - Study 50, up to 18 weeks treatment
  - Study 16, up to 24 weeks treatment
- the add-on studies to
  - metformin (Study 17), up to 24 weeks treatment
  - pioglitazone (Study 15), up to 24 weeks treatment
  - sulphonylurea (Study 35), up to 18 weeks treatment
  - the combination of metformin and sulphonylurea (Study 18), up to 24 weeks treatment

The superiority is supported by sensitivity analyses and FPG measurement.

The non-inferiority of linagliptin 5 mg treatment against the glimepiride in HbA1c improvement is supported by interim efficacy analysis on Study 20 with a non-inferiority margin 0.35% at Week 52. In fact, linagliptin 5 mg is statistically worse than glimepiride in HbA1c improvement at every time measured up to 78 weeks as well as the FPG measurement at Week 52. Moreover, the hypoglycemia incidence rate in the lina 5 mg treated patients is significantly smaller than that in the glimepiride treated patients. In addition, the weight loss in the lina 5 mg treated patients is significantly more than that in the glimepiride treated patients.

Above results were supported by most subgroup analyses including sex, age (<65, >=65), race (Caucasian, non-Caucasian), regions, PAD (Yes, No), HbA1c baseline level (<8.5, >=8.5), BMI (<30, >=30), and renal impairment (eGFR >=90, 60 to <90, <60).

While some subgroup results do not support the superiority of lina 5 mg over placebo group, the forest plot of the 4 pivotal studies does (see Appendix II).

There appears to be no interaction between the baseline HbA1c level and the corresponding HbA1c changes from the baseline in each of the seven studies reviewed here.

Safety

There is no remarkable difference in the trends of time courses on the safety endpoints identified by FDA medical officer between treatments groups of SAF-2 as well as SAF-4.

5.2 Conclusions and Recommendations

Efficacy

Based on collective evidence of the 7 studies analyzed, this reviewer concludes that data from these studies submitted by the sponsor are supportive to the efficacy claim of lina 5 mg treatment on T2DM patients population in.

Reference ID: 2917049

The non-inferiority of linagliptin 5 mg treatment against the glimepiride in HbA1c improvement is supported by a non-inferiority margin 0.35% in the interim efficacy analysis after 52 weeks treatment. In fact, linagliptin 5 mg is statistically worse than glimepiride in HbA1c improvement at every time measured up to 78 weeks as well as the FPG meatrurement at Week 52. Moreover, the hypoglycemia incidence rate in the lina 5 mg treated patients is significantly smaller than that in the glimepiride treated patients. In addition, the weight loss in the lina 5 mg treated patients is significantly more than that in the glimepiride treated patients.

Safety

There appear to be no major differences between the trends of time course on the selected safety endpoints by FDA medical officer in comparing lina 5 mg treated patients to placebo treated patients (SAF-2) as well as to glimepiride treated patients (SAF-4). The selected safety endpoints do not include the major adverse cardiovascular events (MACE) which were reviewed by statisticians in the Division of Biometrics 7.

5.3 Labelling Comments

ref. Sponsor's Proposed Labeling section 14

(b) (4)

Reference ID: 2917049

APPENDIX

Appendix I: List of Abbreviations and Definitions of Terms

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase (SGPT)
ANCOVA	Analysis of covariance
ASA	Acetyl salicylic acid (aspirin)
AST	Aspartate transaminase (SGOT)
AUC	Area under the concentration-time curve
BI	Boehringer Ingelheim
BMI	Body mass index
BRPM	Blinded report planning meeting
CEC	Clinical event committee
CK	Creatinine kinase
CK-MB	Creatinine kinase isoenzyme
CTMF	Clinical trial master file
CTP	Clinical trial protocol
CTR	Clinical trial report
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl-peptidase 4
eCcr	Estimated creatinine clearance rate
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EDTA	Ethylenediaminetetraacetic acid
EMEA	European Medicines Agency
EQ-5D	Standardised instrument for use as a measure of health outcome
FAS	Full analysis set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GGT	γ-Glutamyl-transferase
GCP	Good Clinical Practice
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1
GOD	Glucose Oxidase
h	hour
HbA_{1c}	Glycosylated haemoglobin
HBGM	Home blood glucose monitoring
HCRU	Health care resource utilisation
HDL	High density lipoprotein
HPLC	High-performance liquid chromatography
HrQoL	Health-related Quality of Life
ICH	International Conference on Harmonisation

Reference ID: 2917049

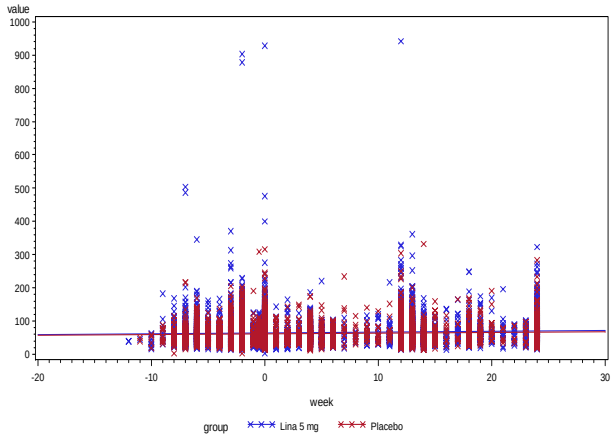
IEC	Independent Ethics Committee
INN	International non-proprietary name
IRB	Institutional Review Board
ISF	Investigator site file
IVRS	Interactive voice response system
IWRS	Interactive web response system
Kg	Kilogramme
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LOCF-ROC	Last observation carried forward after rescue medication
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Myocardial infarction
mL	Millilitre
m	metre
MMRM	Mixed model for repeated measurements
MRI	Magnetic resonance imaging
n.a.	Not applicable
NaF	Sodium fluoride
No.	Number
OC	Observed cases
PCSA	Possibly clinically significant abnormality
P-gp	P-glycoprotein
PPS	Per-protocol set
PT	Preferred term
PV	Protocol violation
SAE	Serious adverse event
SE	Standard error
SMQ	Standardised MedDRA query
SOC	System organ class
SOP	Standard operating procedure
T2DM	Type 2 diabetes mellitus
TDMAP	Trial data management and analysis plan
TIA	Transient ischaemic attack
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organisation

Reference ID: 2917049

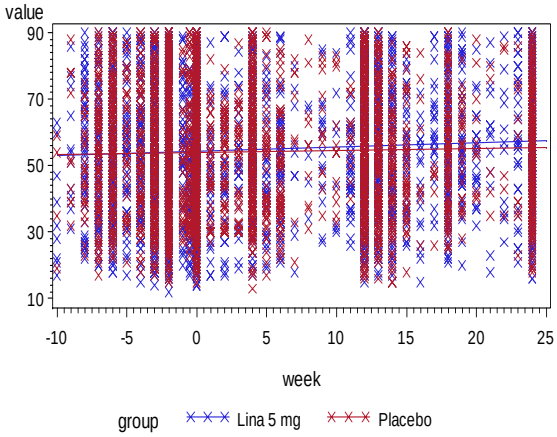
Appendix II: SAF-2 Time Course Plots of Selected Safety Endpoints

SAF-2 Figure 1. The Time Course of Amylase (U/L) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients.

A. Full range



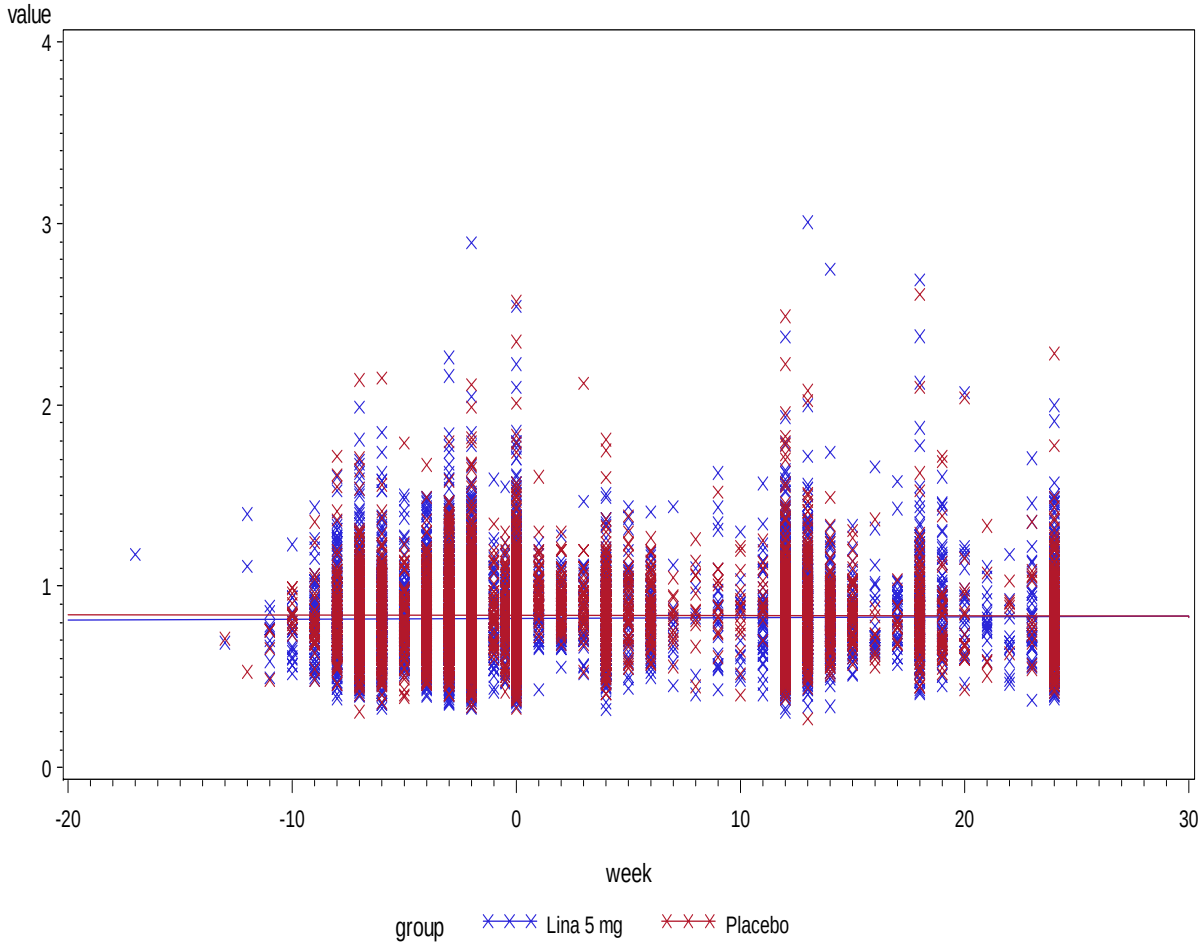
B: Zoom-in




```
Regression equation :  VALUE(group:Lina 5 mg) =  64.0827 + 0.259564*WEEK.
Regression equation :  VALUE(group:Placebo) =  61.60689 + 0.207694*WEEK.
```


Reference ID: 2917049

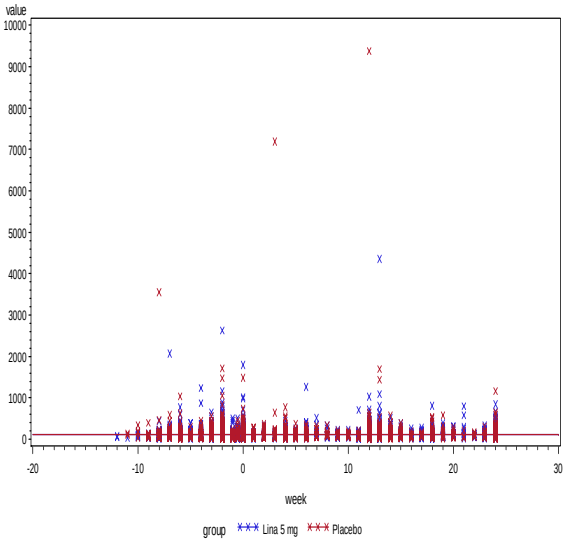
SAF-2 Figure 2. The Time Course of Creatine (mg/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients.



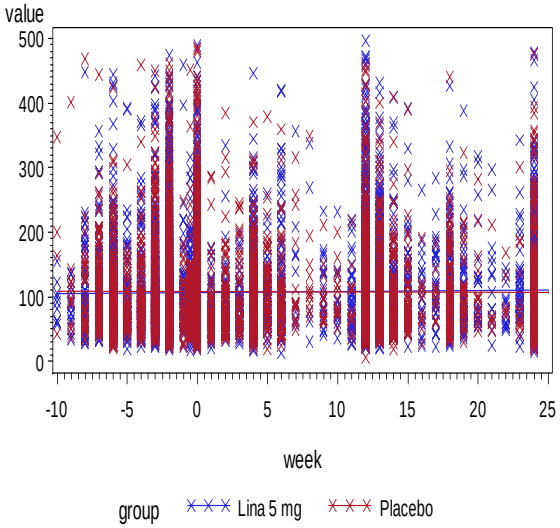

```
Regression equation :  VALUE(group:Lina 5 mg) =  0.822004 + 0.000503*WEEK.
Regression equation :  VALUE(group:Placebo) =  0.836717 - 0.000109*WEEK.
WARNING: Values exist outside the axis range (one >220, one 8-10, one 6-8)
```

SAF-2 Figure 3. The Time Course of Creatine Kinase (U/L) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients.

A. Full range

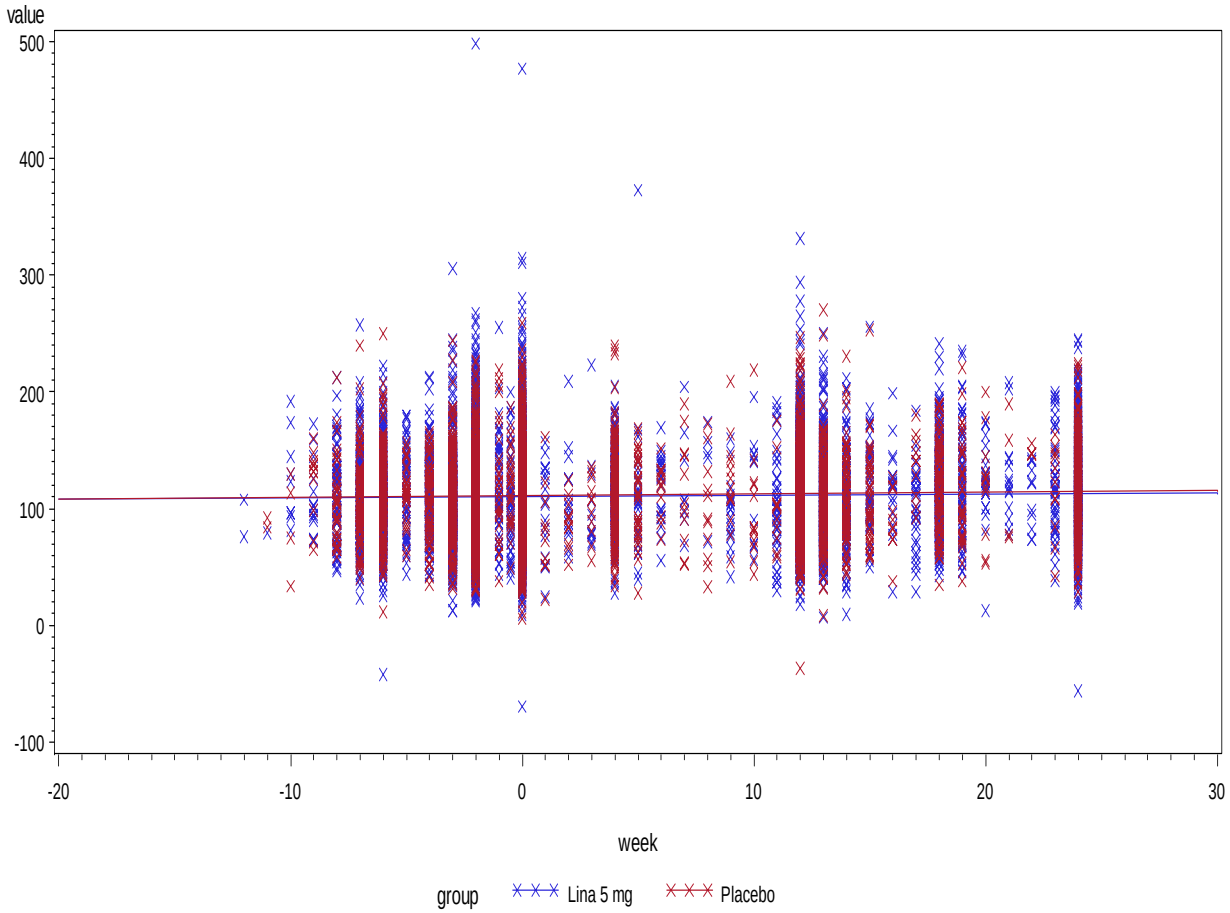


B: Zoom-in



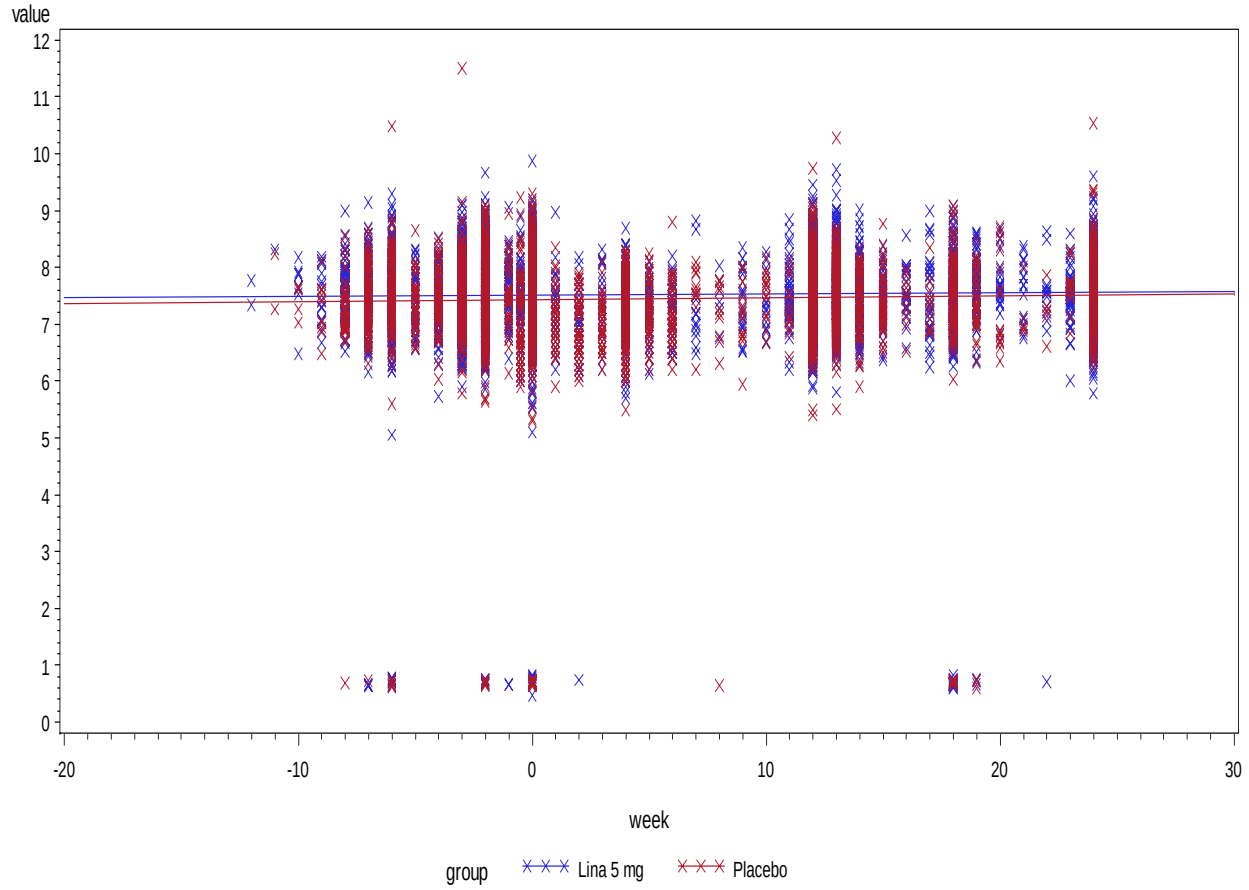

```
Regression equation :  VALUE(group:Lina 5 mg) =  110.5512 + 0.171875*WEEK.
Regression equation :  VALUE(group:Placebo) =  116.4563 + 0.097127*WEEK.
```

SAF-2 Figure 4. The Time Course of LDL Cholesterol (mg/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients.




```
Regression equation :  VALUE(group:Lina 5 mg) =  110.6998 + 0.104502*WEEK.
Regression equation :  VALUE(group:Placebo) =  110.7819 + 0.156447*WEEK.
```

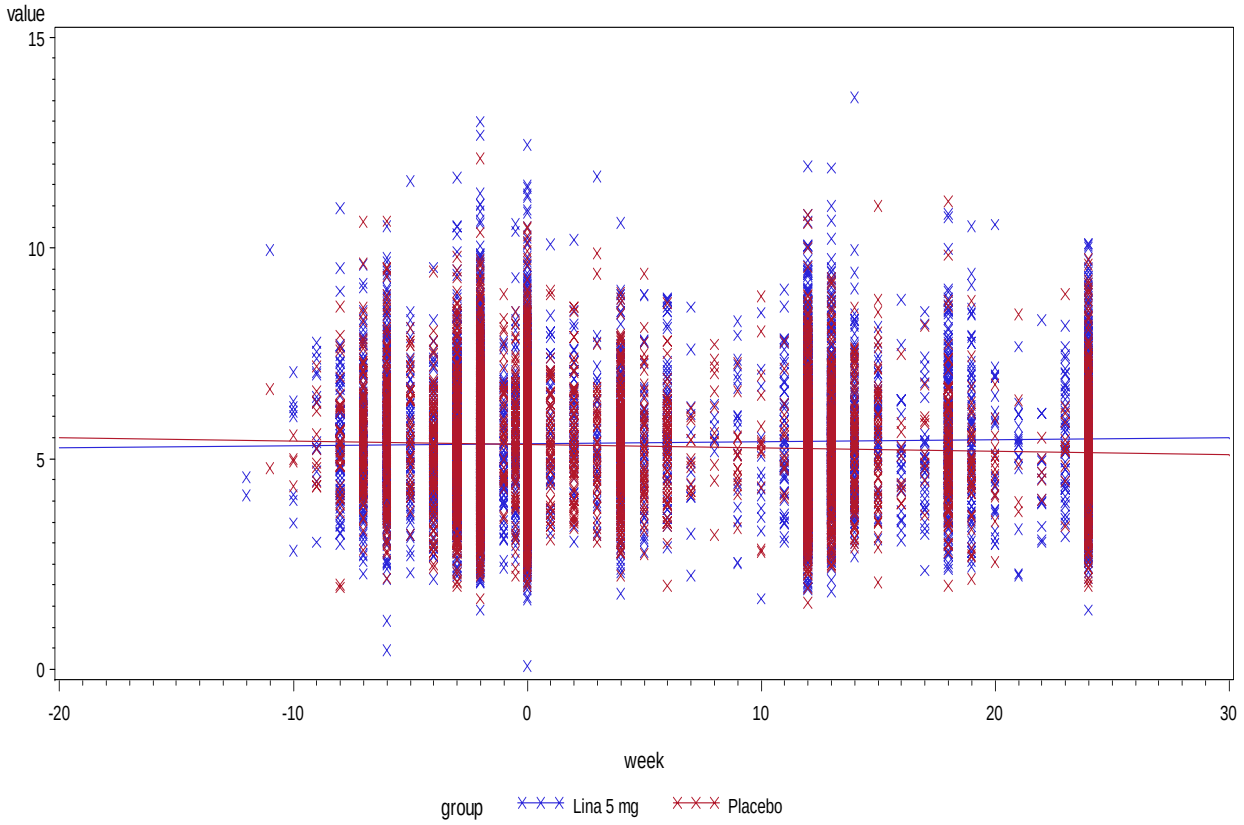
SAF-2 Figure 5. The Time Course of Total Protein (g/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients.




```
Regression equation :  VALUE(group:Lina 5 mg) =  7.507974 + 0.002471*WEEK.
Regression equation :  VALUE(group:Placebo) =  7.425065 + 0.003228*WEEK.
```


Reference ID: 2917049

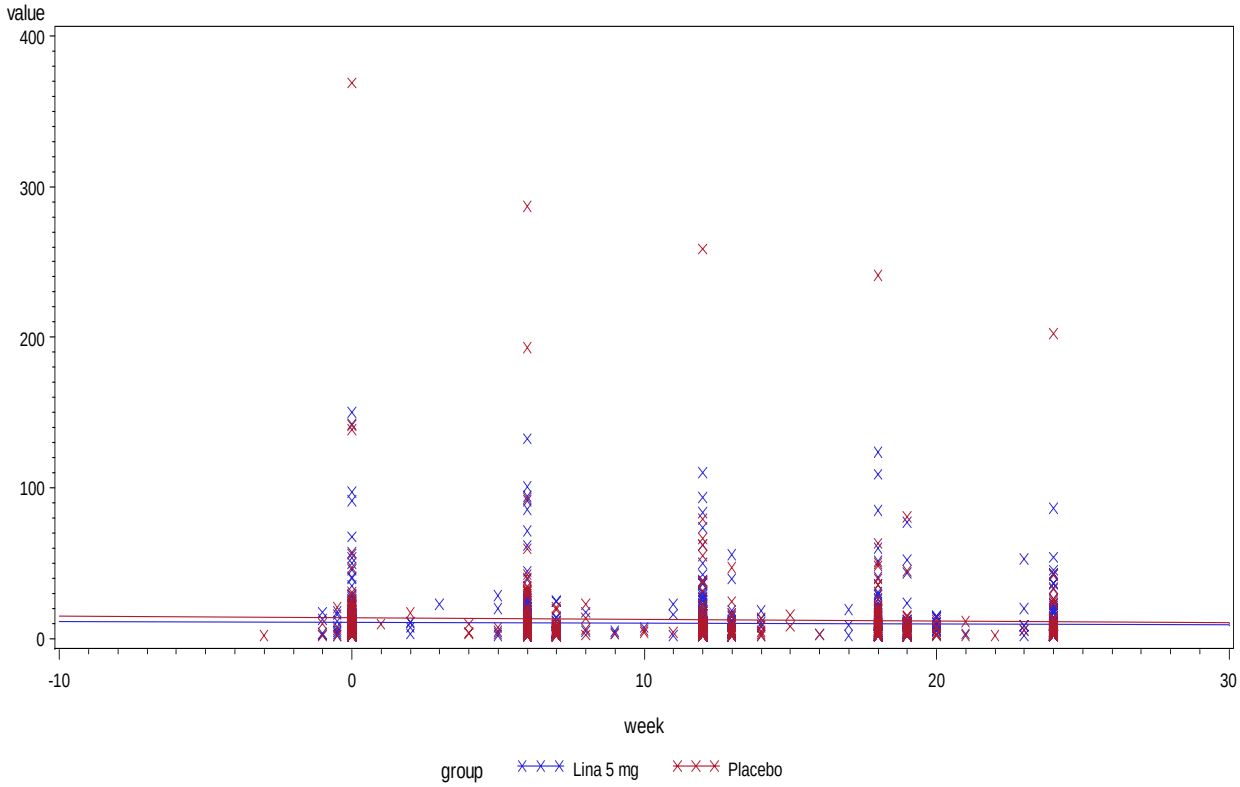
SAF-2 Figure 6. The Time Course of Uric Acid (mg/dL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients.




```
Regression equation :  VALUE(group:Lina 5 mg) =  5.350031 + 0.004533*WEEK.
Regression equation :  VALUE(group:Placebo) =  5.339319 - 0.008044*WEEK.
```


Reference ID: 2917049

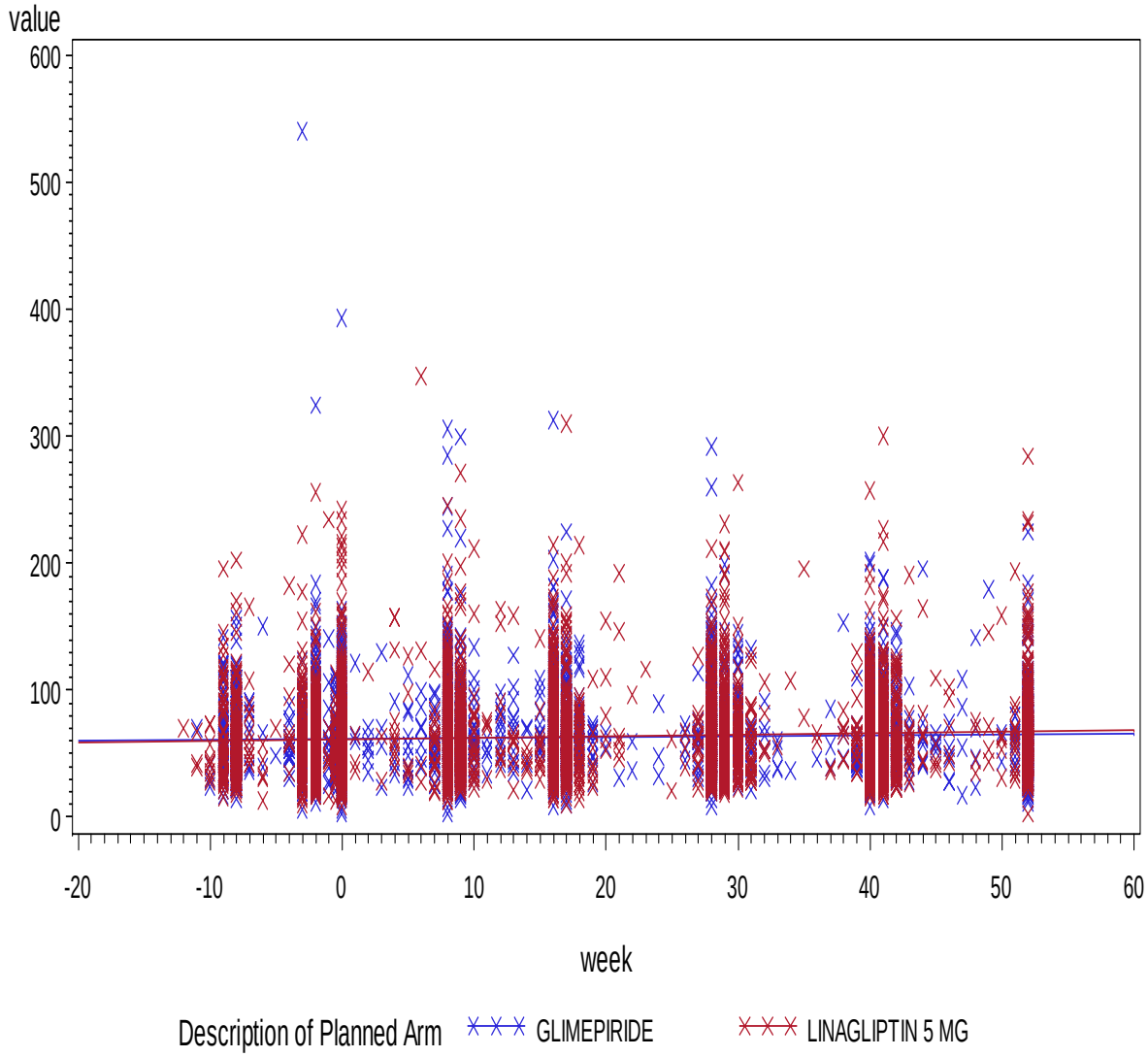
SAF-2 Figure 7. The Time Course of Brian Natriuretic Peptide (pg/mL) for Linagliptin 5 mg and placebo Treatments in SAF-2 Patients.



Regression equation : VALUE(group:Lina 5 mg) = 10.62481 - 0.047485*WEEK.
Regression equation : VALUE(group:Placebo) = 13.75064 - 0.098885*WEEK.
NOTE: Only Study 15 had data of Brian natriuretic peptide: Lina 5mg n=248, Placebo n=123.

Appendix III: SAF-4 Time Course Plots of Selected Safety Endpoints

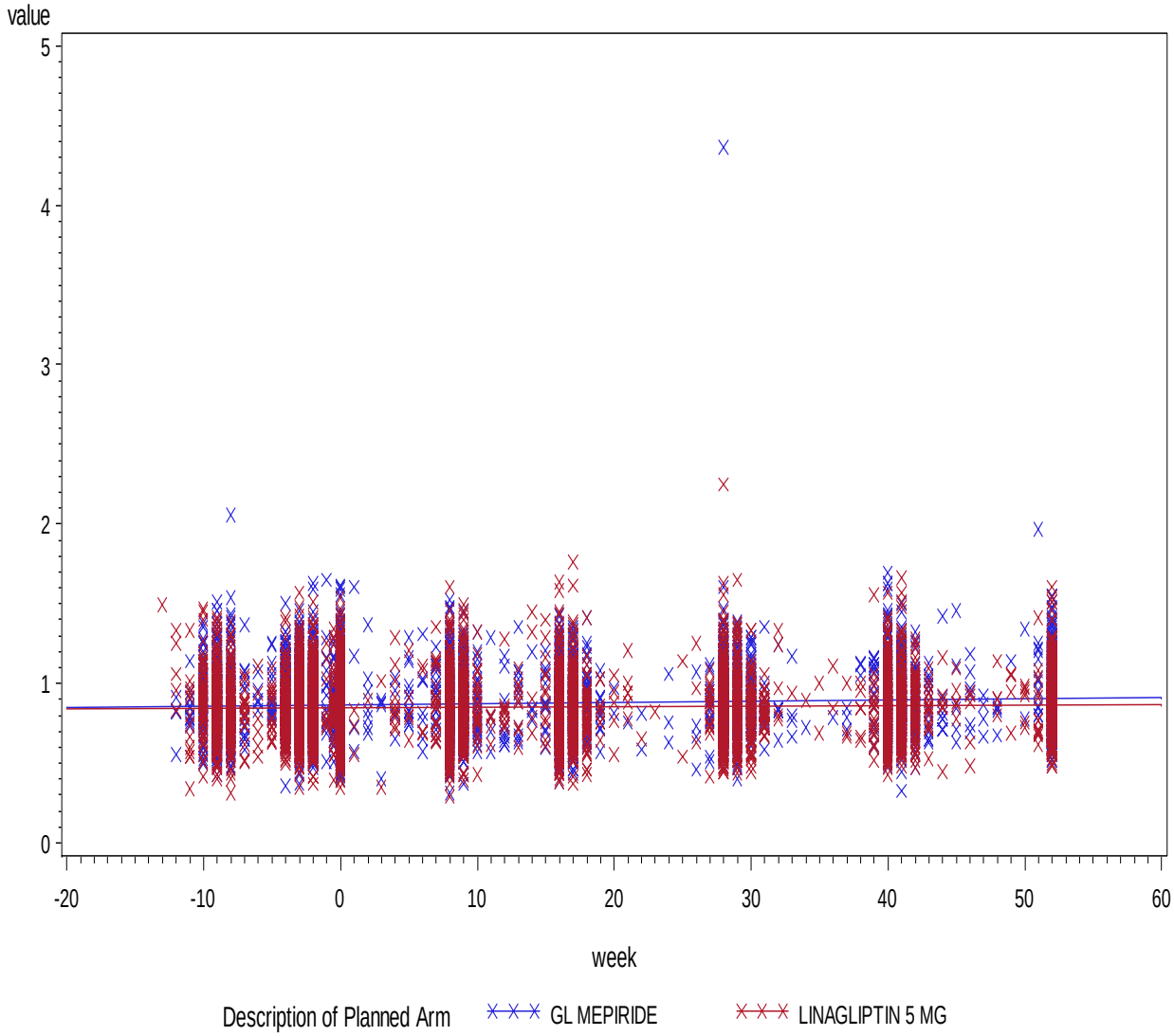
SAF-4 Figure 1. The Time Course of Amylase (U/L) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients.




```
Regression equation :  VALUE(ARM:GLIMEPIRIDE) =  61.47716 + 0.081267*WEEK.
Regression equation :  VALUE(ARM:LINAGLIPTIN 5 MG) =  61.23511 + 0.120085*WEEK.
NOTE: 1 observation(s) contained a MISSING value for the VALUE * WEEK = ARM request.
```


Reference ID: 2917049

SAF-4 Figure 2. The Time Course of Creatinine (mg/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients.

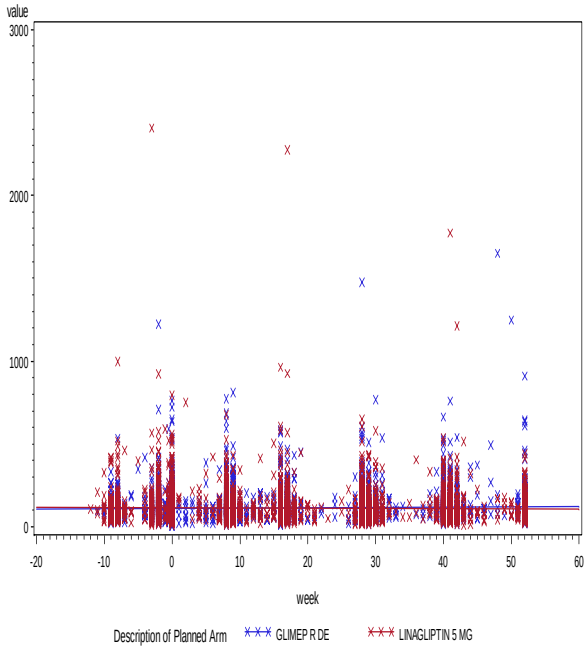


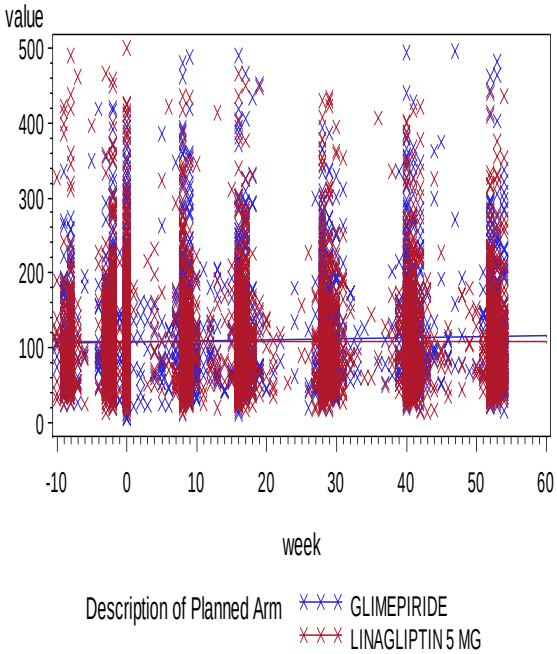

```
Regression equation :  VALUE(ARM:GLIMEPIRIDE) =  0.868051 + 0.000776*WEEK.
Regression equation :  VALUE(ARM:LINAGLIPTIN 5 MG) =  0.850392 + 0.00033*WEEK.
```


Reference ID: 2917049

SAF-4 Figure 3. The Time Course of Creatinine Kinase (U/L) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients.

A. Full range B: Zoom-in

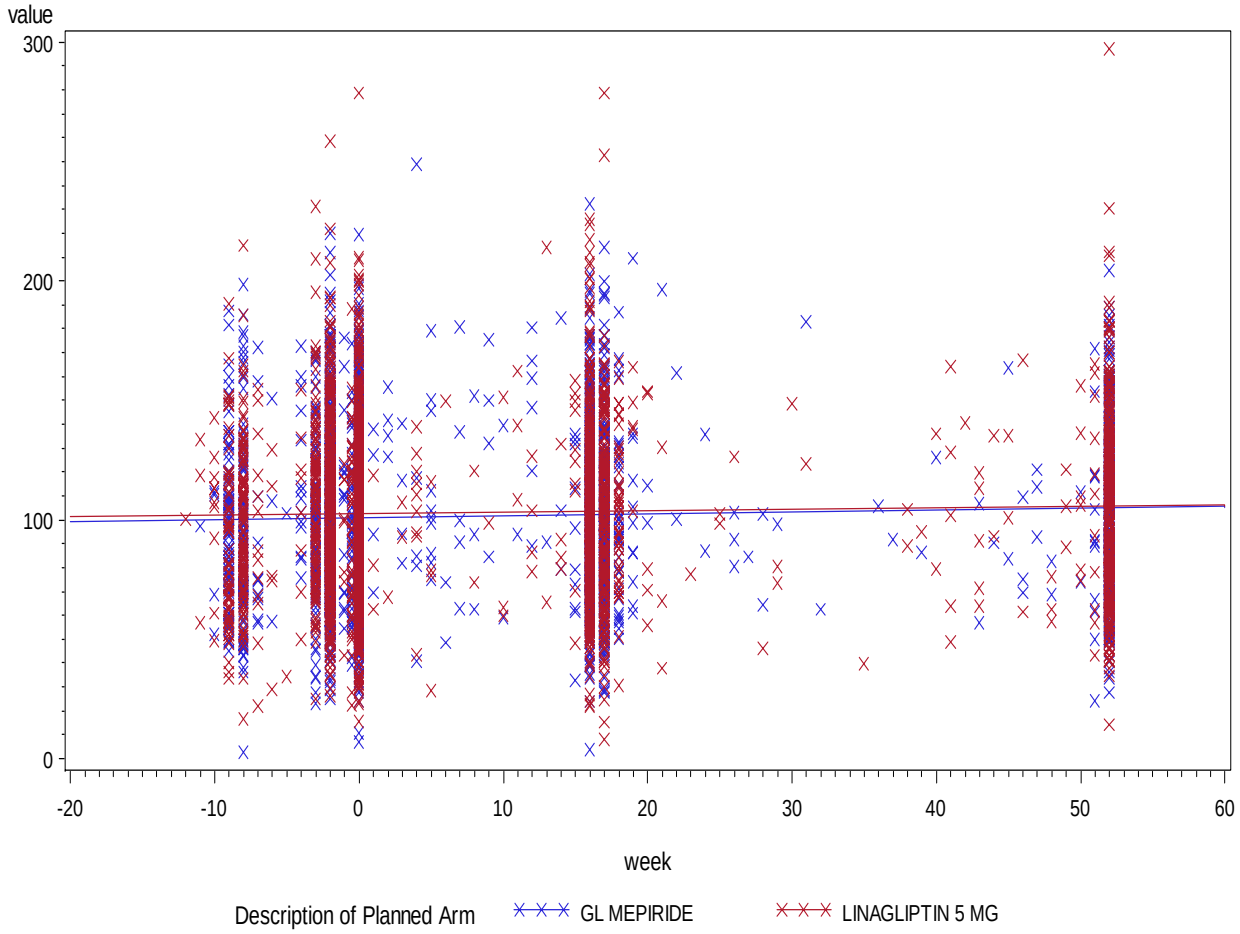





```
Regression equation :  VALUE(ARM:GLIMEPIRIDE) =  110.3781 + 0.240681*WEEK.
Regression equation :  VALUE(ARM:LINAGLIPTIN 5 MG) =  113.888 - 0.082416*WEEK.
```


Reference ID: 2917049

SAF-4 Figure 4. The Time Course of LDL Cholesterol (mg/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients.

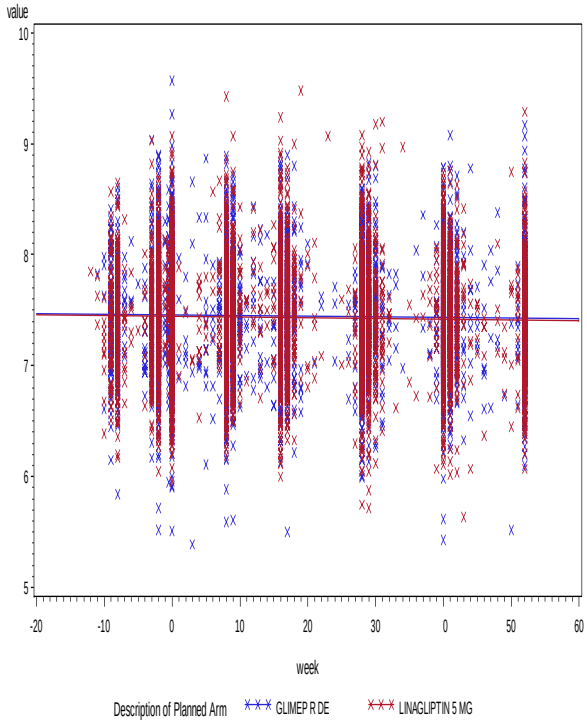


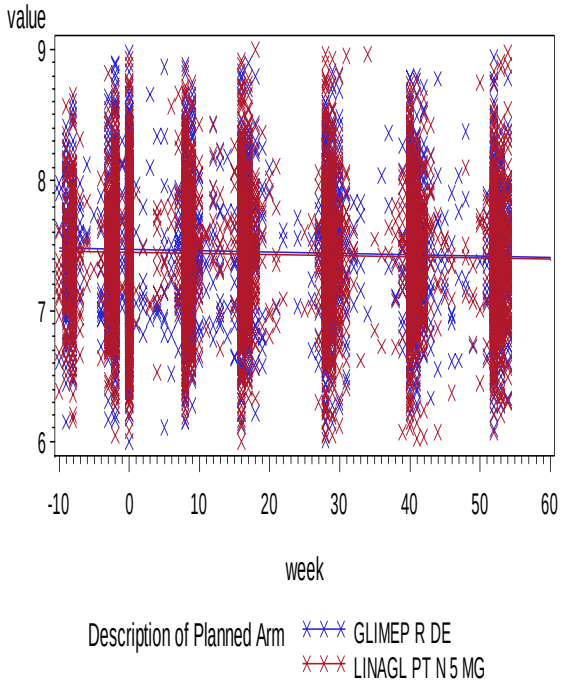

```
Regression equation :  VALUE(ARM:GLIMEPIRIDE) =  101.0532 + 0.080138*WEEK.
Regression equation :  VALUE(ARM:LINAGLIPTIN 5 MG) =  102.4673 + 0.060545*WEEK.
```


Reference ID: 2917049

SAF-4 Figure 5. The Time Course of Total Protein (g/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients.

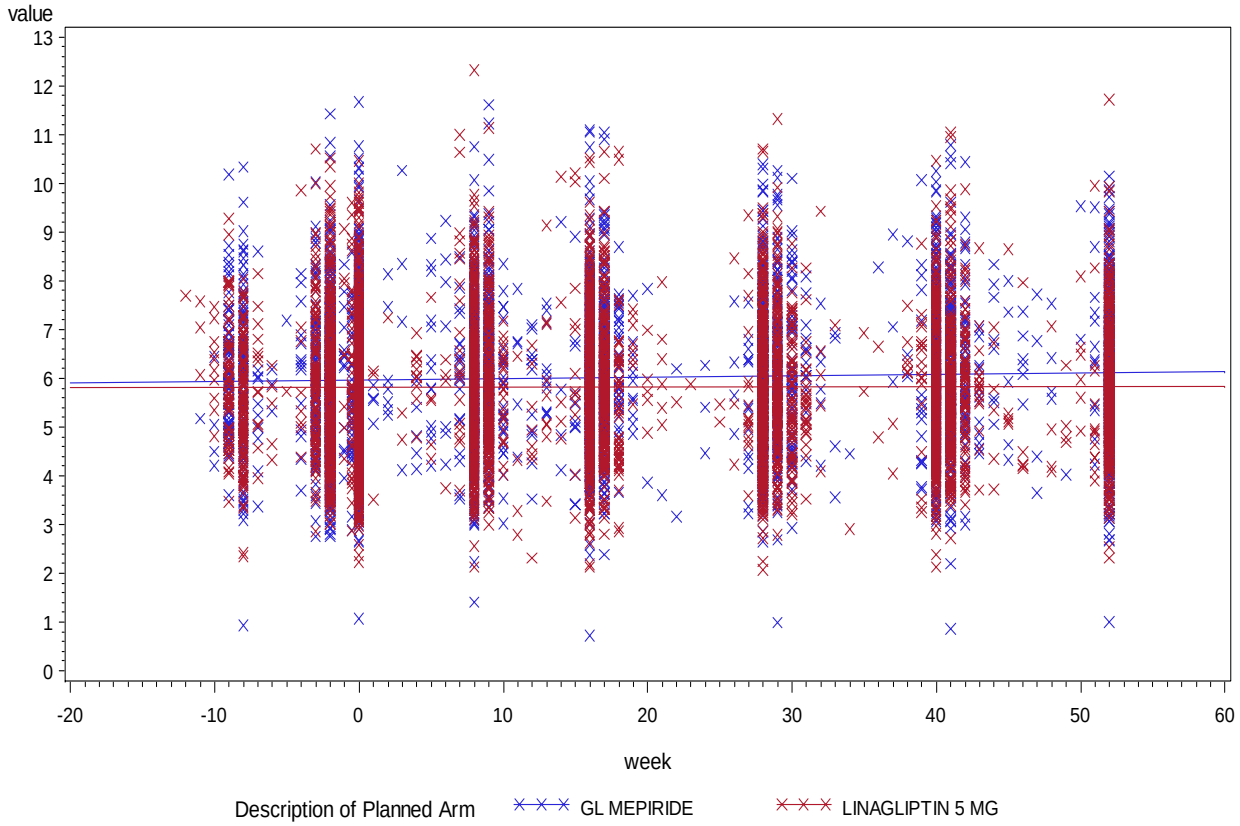
A. Full range B: Zoom-in






```
NOTE: Regression equation :  VALUE(ARM:GLIMEPIRIDE) =  7.458348 - 0.00057*WEEK.
NOTE: Regression equation :  VALUE(ARM:LINAGLIPTIN 5 MG) =  7.445293 - 0.000596*WEEK.
```

SAF-4 Figure 6. The Time Course of Uric Acid (mg/dL) for Linagliptin 5 mg and Glimepiride Treatments in SAF-4 Patients.

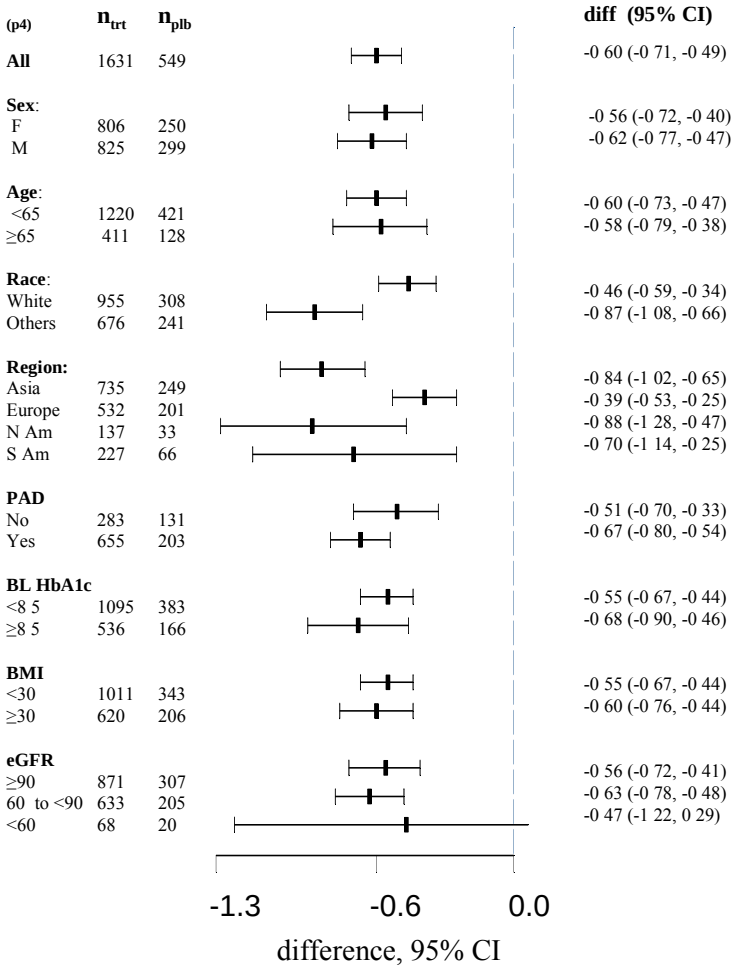



```
Regression equation :  VALUE(ARM:GLIMEPIRIDE) =  5.96244 + 0.003004*WEEK.
Regression equation :  VALUE(ARM:LINAGLIPTIN 5 MG) =  5.810584 + 0.000337*WEEK.
```


Reference ID: 2917049

Appendix IV: Forest plot of pooled pivotal Studies

Meta-analysis of the four pivotal studies (Studies 15 – 18) stratified by study (MMRM).



Reference ID: 2917049

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
03/11/2011

JON T SAHLROOT
03/11/2011

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 20-1280
Drug Name:	BI 1356 BS (Linagliptin)
Indication(s):	104 Week Carcinogenicity Studies in Rats and Mice
Applicant:	Sponsor: Boehringer Ingelheim & Co. Birkendorfer Strasse 65, D-88397 Biberach/Riss, Germany
Documents Reviewed:	Electronic submission: July 2, 2010 Electronic data: July 7, 2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad A. Rahman, Ph.D.
Concurring Reviewer:	Karl K. Lin, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products
Reviewing Pharmacologist:	David Carlson, Ph.D.
Project Manager:	Raymond Chiang
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. ..... Background 3

2. ..... Rat Study 3
2.1. Sponsor's analyses 3
2.1.1. Survival analysis 3
2.1.2. Tumor data analysis 3
2.2. Reviewer's analyses 4
2.2.1. Survival analysis 4
2.2.2. Tumor data analysis 5

3. ..... Mouse Study 6
3.1. Sponsor's analyses 6
3.1.1. Survival analysis 6
3.1.2. Tumor data analysis 6
3.2. Reviewer's analyses 6
3.2.1. Survival analysis 7
3.2.2. Tumor data analysis 7

4. ..... Summary 8

5. ..... Appendix 9

References 21

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of BI 1356 BS (Linagliptin) in rats and mice when administered orally by gavage once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Carlson.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rates as dose increases.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and twenty HsdHan™:Wist (Han Wistar) rats of each sex were randomly assigned to treated and control groups in equal size of 55 animals per group. The dose levels for treated groups were 6, 18, and 60 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The controls received the vehicle (0.5% aqueous hydroxyethylcellulose (Natrosol® 250 HX)) by gavage.

During the administration period all animals were checked daily for survival, general physical condition, and behavior. In addition, a more detailed weekly physical examination, which included palpation, was performed on each animal to monitor general health. Particular attention was paid to any superficial palpable swellings, for which the location, size, consistency, time of first observation and subsequent history were recorded. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment. The body weight of each rat was recorded one week before treatment commenced (Week -1), on the day that treatment commenced (Week 0), at weekly intervals for the first 16 weeks of treatment, every four weeks thereafter and before necropsy..

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method and was presented graphically. Statistical analysis of the data was performed using the log rank test (Mantel 1966) for a dose response relationship across the groups as well as pairwise comparisons of treated groups with the control. If a test for dose response relationship became statistically significant, the highest dosage group was excluded and the dose response relationship (trend) test was repeated, until the test was no longer statistically significant.

Sponsor's findings: Sponsor's analysis showed 69%, 69%, 64%, and 62% survival of male rats and 62%, 62%, 71%, and 58% survival of female rats in their control, low, medium, and high dose groups, respectively. The sponsor analysis did not show statistically significant dose response relationship in mortality among the treated groups, or higher mortality in any of the treated groups compared to the control in either sex.

2.1.2. Tumor data analysis

The sponsor analyzed the tumor data using the life-table analysis method outlined by Peto et al. (1980). For incidental tumors the strata of 1-52, 53-78, 79-92, 93-104 weeks and terminal sacrifice were used to adjust for

mortality differences among the treatment groups. For fatal tumors the weeks of death were used as the strata. The following statistical tests were carried out:

1) One-tailed tests for a dose response relationship using nominal dosage levels and
2) One-tailed pairwise comparisons of each treatment group with the control.

Where the test for dose response relationship was statistically significant, the highest dosage group was excluded and the dose response relationship test was repeated, using a one-tailed test until the test was no longer statistically significant. In general the continuity corrected asymptotic tests were used, however, where there were fewer than ten observed tumor bearing animals, exact one-tailed *p*-values were calculated using the permutation test.

Adjustment for multiple testing: For the adjustment of multiple testing, the sponsor used the method suggested in the draft FDA guidance for the carcinogenicity data analysis (2001). These rules require an initial designation of tumor-types as "common" or "rare". Tumors with an historical frequency greater than 1% were designated as being "common". For this tumor type, a significance level of 0.005 was used for the dose response relationship tests and 0.01 for each pairwise test. Tumors with an historical frequency less than or equal to 1% were designated as being "rare". For this tumor type, a significance level of 0.025 was used for the dose response relationship tests and 0.05 for each pairwise test.

Sponsor's findings: Sponsor's analyses did not show statistically significant dose response relationship among the treated groups, or higher tumor rates in the treated groups compared to the control in any of the tested tumor types in either sex of rats.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analysis were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed 69%, 69%, 64%, and 62% survival of male rats and 62%, 64%, 71%, and 58% survival of female rats in control, low, medium, and high dose groups, respectively. This reviewer's analysis did not show statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups in either sex.

Reviewer's comment: *The sponsor's calculation showed 62% survivor in female low dose group, while this reviewer's calculation showed 64% survivor. This difference is due to the fact that there was one female rat in low dose group (#350) that died naturally*

during terminal sacrifice weeks. The sponsor did not count it as a survivor while this reviewer counted it as a survivor.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with at least one tumor gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study and/or if each animal develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

Multiple testing adjustment: For the adjustment of multiple testing this reviewer also used the significance levels recommended in the FDA draft guidance (2001) for the carcinogenicity study design and data analysis, namely for dose response relationship use of test levels α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one species; and for the pairwise comparisons the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors for both submissions with two or one species.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following tumor type showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of treated groups and control.

Tumor Type with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons in Rats

Sex	Organ Name	Tumor Name	0 mg Cont N=55	6 mg Low N=55	18 mg Med N=55	60 mg High N=55	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	THYROIDS	C_CELL_ADEN+CAR	7	10	15	9	0.4057	0.2486	0.0392	0.3219

Based on the multiple testing adjustment procedure discussed above, the pairwise comparison of control and medium dose group for the combined incidence of C-Cell adenoma and carcinoma in thyroids is not considered to be statistically significant.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and forty Crl:CD-1(ICR) mice in each sex were randomly assigned to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 8, 25, and 80 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The controls received the vehicle (0.5% aqueous hydroxyethylcellulose (Natrosol® 250 HX)) by gavage.

During the administration period all animals were checked daily for survival, general physical condition, and behavior. In addition, a more detailed weekly physical examination, which included palpation, was performed on each animal to monitor general health. Particular attention was paid to any superficial palpable swellings, for which the location, size, consistency, time of first observation and subsequent history were recorded. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment. The body weight of each rat was recorded one week before treatment commenced (Week -1), on the day that treatment commenced (Week 0), at weekly intervals for the first 16 weeks of treatment, every four weeks thereafter and before necropsy.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as were used to analyze the survival data from the rat study.

Sponsor's findings: Sponsor's analysis showed 48%, 50%, 58%, and 65% survival of male mice and 47%, 33%, 47%, and 32% survival of female mice in control, low, medium, and high dose groups, respectively. The sponsor analysis showed statistically significant positive dose response relationship in survival in male mice, indicating higher survival in the high dose group.

3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed using the same statistical methodologies as were used to analyze the tumor data from the rat study.

Sponsor's findings: Sponsor's analyses did not show statistically significant dose response relationship among the treated groups, or higher tumor rates in the treated groups compared to the control in any of the tested tumor types in either sex of mice.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as he used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed 50%, 50%, 58%, and 68% survival of male mice, and 47%, 35%, 47%, and 33% survival of female mice in control, low, medium, and high dose groups, respectively. This reviewer's analysis did not show statistically significant dose response relationship in the mortality across treatment groups in either sex. The pairwise comparisons showed statistically significant decreased mortality in the high dose group compared to the control.

Reviewer's comment: *As mentioned, in control, low, medium, and high dose groups the sponsor's calculation showed 48%, 50%, 58%, and 65% survival of male mice and 47%, 33%, 47%, and 32% survival of female mice, while this reviewer's calculation showed 50%, 50%, 58%, and 68% survival of male mice, and 47%, 35%, 47%, and 33% survival of female mice. Clearly, there are some discrepancies between the sponsor's count and this reviewer's count. These discrepancies are due to the fact that there was one male mouse in control group (#19) and two male mice in high dose group (#309 and #324) that died naturally during terminal sacrifice weeks. Also there was one female mouse in low dose group (#476) and one male mouse in high dose group (#632) that died naturally during terminal sacrifice weeks. The sponsor did not count these animals as a survivor, while this reviewer counted them as a survivor.*

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: Following tumor type showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of treated groups and control.

Tumor Type with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons in Mice

Sex	Organ Name	Tumor Name	0 mg Cont N=58	8 mg Low N=60	25 mg Med N=60	80 mg High N=60	P_Value Dose Resp	C vs L	C vs M	C vs H
Male	LUNG	BRONCH_ADENO+ADENOCA	15	24	27	24	0.3824	0.0779	0.0341	0.1789
Female	H-POIETIC TUMOUR	LYMPHOMA	6	11	11	22	<0.001*	0.0918	0.1012	<0.001*
	WHOLE_BODY	HAEMANG+HAEMANG_SARC	2	7	2	1	0.9114	0.0461	0.6372	0.8407
		LYMPHOMAS#	6	11	11	22	<0.001*	0.0918	0.1012	<0.001*

On the request of the reviewing pharmacologist this reviewer analyzed the whole body incidence of lymphomas, however this tumor type was found only on one organ (actually as only one class) namely as H-Poietic tumor

Based on the multiple testing adjustment procedure discussed in the rat data analysis section, the dose response relationship in the incidence rate of H-Poietic tumor/Lymphoma (also whole body/Lymphoma) is

considered to be statistically significant. Also by pairwise comparisons the increased incidence of this tumor type in the high dose group is considered to be statistically significant compared to the control.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of BI 1356 BS (Linagliptin) in rats and mice when administered orally by gavage once daily at appropriate drug levels for about 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and twenty HsdHan™:Wist (Han Wistar) rats of each sex were randomly assigned to treated and control groups in equal size of 55 animals per group. The dose levels for treated groups were 6, 18, and 60 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The controls received the vehicle (0.5% aqueous hydroxyethylcellulose (Natrosol® 250 HX)) by gavage.

The tests did not show statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups in either sex. The tests did not show statistically significant positive dose response relationship in any of the tested tumor types. The pairwise comparisons also did not show statistically significant increased incidence of any tumor type in any of the treated groups compared to the control.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and forty Crl:CD-1(ICR) mice in each sex were randomly assigned to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 8, 25, and 80 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The controls received the vehicle (0.5% aqueous hydroxyethylcellulose (Natrosol® 250 HX)) by gavage.

The tests did not show statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons showed statistically significant decreased mortality in the high dose group compared to the control. The testes showed statistically significant dose response relationship in the incidence rate of H-Poietic tumor/Lymphoma in female mice. The pairwise comparison showed statistically significant increased incidence of this tumor type in the high dose group is considered to the control.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 20-1280
Dr. Carlson
Mr. Chiang
Dr. Machado
Dr. Lin
Dr. Rahman
MS. Patrician

5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	0 mg|kg|day No. of Death	Cum. %	6 mg|kg|day No. of Death	Cum. %	18 mg|kg|day No. of Death	Cum. %	60 mg|kg|day No. of Death	Cum. %
0 - 52	2	3.64	3	5.45	2	3.64	3	5.45
53 - 78	3	9.09	6	16.36	5	12.73	4	12.73
79 - 91	5	18.18	2	20.00	4	20.00	8	27.27
92 - 104	7	30.91	6	30.91	9	36.36	6	38.18
Ter. Sac.	38	69.09	38	69.09	35	63.64	34	61.82
Total	N=55		N=55		N=55		N=55	

Table 1B: Intercurrent Mortality Rate
Female Rats

Week	0 mg|kg|day No. of Death	Cum. %	6 mg|kg|day No. of Death	Cum. %	18 mg|kg|day No. of Death	Cum. %	60 mg|kg|day No. of Death	Cum. %
0 - 52	.	.	3	5.45	1	1.82	3	5.45
53 - 78	2	3.64	4	12.73	7	14.55	4	12.73
79 - 91	8	18.18	5	21.82	3	20.00	9	29.09
92 - 104	11	38.18	8	36.36	5	29.09	7	41.82
Ter. Sac.	34	61.82	35	63.64	39	70.91	32	58.18
Total	N=60		N=60		N=60		N=60	

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.3597
Homogeneity	Log-Rank	0.8028

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.4836
Homogeneity	Log-Rank	0.6093

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Cont N=55	6 mg Low N=55	18 mg Med N=55	60 mg High N=55	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ABDOMEN	LIPOMA	0	1	0	0	0.7432	0.4946	.	.
	SARCOMA, NOS	1	1	0	0	0.9330	0.7419	1.0000	1.0000
ADRENALS	COMPLEX MEDULLARY TU	0	0	1	0	0.4918	.	0.4946	.
	CORTICAL ADENOMA	1	2	1	0	0.8683	0.4918	0.7473	1.0000
	CORTICAL CARCINOMA	0	1	0	0	0.7432	0.4946	.	.
	GANGLIONEUROMA	0	1	0	0	0.7432	0.4946	.	.
	PHAEOCHROMOCYTOMA	1	1	2	1	0.4795	0.7473	0.4918	0.7360
BRAIN	ASTROCYTOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	GRANULAR CELL TUMOUR	0	1	0	0	0.7432	0.4946	.	.
		1	1	2	0	0.7787	0.7473	0.4918	1.0000
DUODENUM	LEIOMYOMA	2	0	0	0	1.0000	1.0000	1.0000	1.0000
H-POIETIC TUMOU	LYMPHOCYTIC / LYMPHO	1	1	0	1	0.5185	0.7474	1.0000	0.7363
	PLEOMORPHIC LYMPHOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
HEAD	SQUAMOUS CELL CARCIN	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	ZYMBAL'S GLAND CARCI	1	1	0	1	0.5132	0.7419	1.0000	0.7305
HEART	MALIGNANT SCHWANNOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
LIVER	HEPATOCELLULAR CARCI	1	0	0	0	1.0000	1.0000	1.0000	1.0000
LN MESENTERIC	HAEMANGIOMA	4	2	3	1	0.8716	0.8933	0.7736	0.9670
LT INCISOR - LS	SQUAMOUS CELL CARCIN	0	1	0	0	0.7432	0.4946	.	.
LUNGS + BRONCHI	BRONCHIOLOALVEOLAR A	0	0	1	1	0.1783	.	0.4946	0.4835
MAMMARY	FIBROMA	2	1	0	0	0.9839	0.8750	1.0000	1.0000
	LIPOMA	0	1	0	0	0.7432	0.4946	.	.
NASAL TURBINATE	SQUAMOUS CELL CARCIN	0	0	0	1	0.2404	.	.	0.4835
PANCREAS	ISLET CELL ADENOMA	2	0	1	2	0.2798	1.0000	0.8750	0.6663
	ISLET CELL CARCINOMA	0	1	0	0	0.7432	0.4946	.	.
PARATHYROIDS	CHIEF CELL ADENOMA	0	1	0	1	0.2999	0.4946	.	0.4835
PERIPHERAL NERV	SCHWANNOMA	0	0	0	1	0.2446	.	.	0.4891
PINNAE	FIBROSARCOMA	0	0	1	0	0.4918	.	0.4946	.
PITUITARY	ADENOMA, PARS DISTA	22	14	23	20	0.4132	0.9648	0.6341	0.7282
	ADENOMA, PARS INTERM	1	2	0	0	0.9344	0.4918	1.0000	1.0000
PREPUTIAL GLAND	SQUAMOUS CELL CARCIN	2	1	0	0	0.9831	0.8710	1.0000	1.0000

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Cont N=55	6 mg Low N=55	18 mg Med N=55	60 mg High N=55	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
PROSTATE	ADENOMA	0	0	1	0	0.4918	.	0.4946	.
SEMINAL VESICLE	ADENOMA	0	1	0	0	0.7432	0.4946	.	.
SKELETAL MUSCLE	HAEMANGIOMA	0	0	1	1	0.1818	.	0.4946	0.4891
SKIN	BASAL CELL TUMOUR	0	1	1	0	0.6133	0.4946	0.4946	.
	BENIGN FIBROUS HISTI	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	FIBROMA	0	4	1	2	0.3783	0.0585	0.4946	0.2310
	KERATOACANTHOMA	8	3	5	3	0.8632	0.9702	0.8673	0.9676
	LIPOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	LIPOSARCOMA	0	0	0	1	0.2446	.	.	0.4891
	SEBACEOUS CELL ADENO	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	SQUAMOUS CELL CARCIN	0	2	1	0	0.7224	0.2419	0.4946	.
	SQUAMOUS CELL PAPILL	1	0	0	1	0.4241	1.0000	1.0000	0.7360
SPLEEN	HAEMANGIOMA	0	0	1	0	0.4918	.	0.4946	.
	STROMAL TUMOUR	0	0	0	1	0.2404	.	.	0.4835
TESTES	INTERSTITIAL (LEYDIG	1	2	0	0	0.9344	0.4918	1.0000	1.0000
THYMUS	HAEMANGIOSARCOMA	0	0	1	0	0.4918	.	0.4946	.
	THYMOMA (LYMPHOID)	0	3	1	0	0.8188	0.1170	0.4946	.
THYROIDS	C-CELL ADENOMA	6	9	13	8	0.4123	0.2571	0.0614	0.3368
	C-CELL CARCINOMA	1	2	2	1	0.5800	0.4918	0.4918	0.7360
	C_CELL_ADEN+CAR	7	10	15	9	0.4057	0.2486	0.0392	0.3219
	FOLLICULAR CELL ADEN	6	1	1	3	0.6106	0.9928	0.9928	0.9048
	FOLLICULAR CELL CARC	1	0	0	1	0.4241	1.0000	1.0000	0.7360
WHOLE_BODY	HAEMANG+HAEMANG_SARC	4	2	5	2	0.7172	0.8933	0.4862	0.8881
	LYMPHOMAS	2	1	0	1	0.6574	0.8711	1.0000	0.8626

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats

Organ Name	Tumor Name	0 mg Cont N=55	6 mg Low N=55	18 mg Med N=55	60 mg High N=55	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ABDOMEN	MESOTHELIOMA	0	0	0	1	0.2391	.	.	0.4835
ADIPOSE TISSUE	HIBERNOMA	0	0	0	1	0.2391	.	.	0.4835
ADRENALS	CORTICAL ADENOMA	1	2	1	1	0.5886	0.5000	0.7527	0.7360
	MALIGNANT PHAEOCHROM	0	1	0	0	0.7459	0.5000	.	.
BRAIN	ASTROCYTOMA	0	1	0	0	0.7446	0.4946	.	.
	GRANULAR CELL TUMOUR	2	0	1	1	0.5553	1.0000	0.8750	0.8623
	OLIGODENDROGLIOMA	0	0	0	1	0.2432	.	.	0.4891
	PINEAL GLAND CARCINO	0	1	0	0	0.7446	0.4946	.	.
BROWN ADIP TISS	HIBERNOMA	0	0	0	1	0.2391	.	.	0.4835
BUCCAL CAVITY	SQUAMOUS CELL CARCIN	0	0	0	1	0.2391	.	.	0.4835
CLITORAL GLANDS	SQUAMOUS CELL CARCIN	1	1	2	0	0.7796	0.7473	0.5000	1.0000
	SQUAMOUS CELL PAPILL	0	0	1	0	0.4946	.	0.5000	.
H-POIETIC TUMOU	LYMPHOCYTIC / LYMPHO	0	0	1	0	0.4973	.	0.5053	.
HEAD	YOLK SAC CELL TUMOUR	0	1	0	0	0.7459	0.5000	.	.
	ZYMBAL'S GLAND CARCI	0	0	0	1	0.2391	.	.	0.4835
JEJUNUM	LEIOMYOMA	0	1	0	0	0.7446	0.4946	.	.
LIVER	CHOLANGIOMA	0	0	0	1	0.2391	.	.	0.4835
	HEPATOCELLULAR CARCI	0	1	0	0	0.7446	0.4946	.	.
LN MESENTERIC	HAEMANGIOMA	1	3	1	0	0.9111	0.3002	0.7527	1.0000
MAMMARY	ADENO+ADENO_CARC+FOB	4	3	6	2	0.7626	0.7736	0.3699	0.8826
	FIBROMA	0	1	0	0	0.7459	0.5000	.	.
	MAMMARY ADENOCARCINO	1	2	4	2	0.3869	0.4918	0.1807	0.4750
	MAMMARY ADENOMA	3	1	2	0	0.9401	0.9389	0.8193	1.0000
	MAMMARY FIBROADENOMA	10	18	14	15	0.2836	0.0576	0.2400	0.1450
NASAL TURBINATE	SQUAMOUS CELL CARCIN	1	0	0	0	1.0000	1.0000	1.0000	1.0000
OVARIES	GRANULOSA CELL TUMOU	0	0	0	1	0.2391	.	.	0.4835
		4	1	2	0	0.9709	0.9688	0.8933	1.0000
	THECAL CELL TUMOUR	0	1	0	0	0.7446	0.4946	.	.
	TUBULAR ADENOMA	0	0	0	1	0.2391	.	.	0.4835
PANCREAS	ISLET CELL ADENOMA	1	1	1	0	0.8198	0.7419	0.7474	1.0000
	ISLET CELL CARCINOMA	0	1	0	0	0.7459	0.5000	.	.
PITUITARY	ADENOMA, PARS DISTA	34	37	38	30	0.8213	0.1933	0.2194	0.6951
	ADENOMA, PARS INTERM	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	CARCINOMA, PARS DIST	2	1	0	1	0.6517	0.8750	1.0000	0.8623

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Cont N=55	6 mg Low N=55	18 mg Med N=55	60 mg High N=55	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
SKIN	HAEMANGIOSARCOMA	0	0	1	0	0.4946	.	0.5000	.
	KERATOACANTHOMA	0	1	1	1	0.2823	0.4946	0.5000	0.4835
	SQUAMOUS CELL CARCIN	0	0	0	1	0.2391	.	.	0.4835
	SQUAMOUS CELL PAPILL	0	0	1	0	0.4946	.	0.5000	.
SKIN+SUBCUTIS	SQ_C_PAP+CAR+KARAT	0	0	1	1	0.1790	.	0.5000	0.4835
THYMUS	MALIGNANT THYMOMA	0	1	0	0	0.7446	0.4946	.	.
	THYMOMA (LYMPHOID)	4	4	1	5	0.2536	0.6429	0.9721	0.4576
THYROIDS	C-CELL ADENOMA	13	18	16	11	0.7739	0.1735	0.3052	0.6566
	C-CELL CARCINOMA	0	1	0	1	0.2992	0.4946	.	0.4835
	C_CELL_ADEN+CAR	13	19	16	12	0.7148	0.1248	0.3052	0.5602
	FOLLICULAR CELL ADEN	2	1	2	2	0.3819	0.8750	0.6916	0.6663
	FOLLICULAR CELL CARC	0	0	1	0	0.4946	.	0.5000	.
UTERINE CERVIX	ENDOMETRIAL POLYP	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	MALIGNANT SCHWANNOMA	0	1	1	0	0.6147	0.4946	0.5000	.
UTERUS	ENDOMETRIAL ADENOCAR	2	1	2	0	0.8776	0.8710	0.6835	1.0000
	ENDOMETRIAL POLYP	3	3	3	6	0.8852	0.6513	0.6513	0.2114
WHOLE_BODY	HAEMANG+HAEMANG_SARC	1	3	2	0	0.8909	0.3002	0.5000	1.0000
	LYMPHOMAS	0	0	1	0	0.4973	.	0.5053	.

Table 4A: Intercurrent Mortality Rate in Male Mice

Week	0 mg|kg|day No. of Death	Cum. %	8 mg|kg|day No. of Death	Cum. %	25 mg|kg|day No. of Death	Cum. %	80 mg|kg|day No. of Death	Cum. %
0 - 52	7	11.67	3	5.00	1	1.67	1	1.67
53 - 78	8	25.00	12	25.00	9	16.67	4	8.33
79 - 91	3	30.00	5	33.33	7	28.33	8	21.67
92 - 104	12	50.00	10	50.00	8	41.67	6	31.67
Ter. Sac.	30	50.00	30	50.00	35	58.33	41	68.33
Total	N=60		N=60		N=60		N=60	

Table 4B: Intercurrent Mortality Rate Female Mice

Week	0 mg|kg|day No. of Death	Cum. %	8 mg|kg|day No. of Death	Cum. %	25 mg|kg|day No. of Death	Cum. %	80 mg|kg|day No. of Death	Cum. %
0 - 52	2	3.33	7	11.67	8	13.33	6	10.00
53 - 78	8	16.67	13	33.33	11	31.67	14	33.33
79 - 91	9	31.67	11	51.67	6	41.67	8	46.67
92 - 104	13	53.33	8	65.00	7	53.33	12	66.67
Ter. Sac.	28	46.67	21	35.00	28	46.67	20	33.33
Total	N=60		N=60		N=60		N=60	

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.0314
Homogeneity	Log-Rank	0.1823

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.1656
Homogeneity	Log-Rank	0.1397

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=60	8 mg Low N=60	25 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ABDOMEN	ADRENAL CORTICAL ADE	1	0	0	0	1.0000	1.0000	1.0000	1.0000
ADIPOSE TISSUE	HAEMANGIOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	HAEMANGIOSARCOMA	0	0	0	1	0.2751	.	.	0.5361
ADRENALS	CORTICAL ADENOMA	1	0	1	0	0.7772	1.0000	0.7686	1.0000
	PHAEOCHROMOCYTOMA	0	0	0	1	0.2713	.	.	0.5312
	SUBCAPSULAR CELL ADE	2	4	5	6	0.1641	0.3383	0.2543	0.1863
ALL_BONES	CHONDROM+OSTEOSAR+OS	1	0	0	0	1.0000	1.0000	1.0000	1.0000
BRAIN	MENINGIOMA	0	1	0	0	0.7619	0.5000	.	.
CAECUM	ADENOCARCINOMA	0	0	0	1	0.2751	.	.	0.5361
COLON	POLYPOPID ADENOMA	0	1	0	0	0.7619	0.5000	.	.
DUODENUM	ADENOCARCINOMA	0	0	1	0	0.5266	.	0.5161	.
	ADENOMA	0	0	0	1	0.2713	.	.	0.5312
EPIDIDYMIDES	INTERSTITIAL (LEYDIG	0	0	0	1	0.2713	.	.	0.5312
FEMUR INC. JOIN	HAEMANGIOMA	1	0	0	1	0.4756	1.0000	1.0000	0.7874
H-POIETIC TUMOU	HISTIOCYTIC SARCOMA	1	1	0	1	0.5734	0.7528	1.0000	0.7874
	LYMPHOMA	11	4	6	0	0.9998	0.9861	0.9508	1.0000
	MALIGNANT MAST CELL	0	1	0	0	0.7619	0.5000	.	.
	MYELOID CELL LEUKAEM	1	1	0	1	0.5734	0.7528	1.0000	0.7874
	PLASMA CELL LYMPHOMA	0	0	1	0	0.5266	.	0.5161	.
HARDERIAN GLAND	ADENOCARCINOMA	0	0	1	1	0.2151	.	0.5161	0.5361
	ADENOMA	7	7	8	4	0.9057	0.5964	0.5362	0.9290
HEART	PARAGANGLIOMA	0	0	0	1	0.2751	.	.	0.5361
	SARCOMA NOS	0	1	0	0	0.7619	0.5000	.	.
KIDNEYS	TUBULAR ADENOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	TUBULAR CARCINOMA	0	0	2	0	0.5342	.	0.2637	.
	TUBULAR_CELL_ADEN+CA	1	0	2	0	0.7233	1.0000	0.5245	1.0000
LIVER	CHOLANGIOCARCINOMA	0	1	0	0	0.7619	0.5000	.	.
	HAEMANGIOMA	2	1	3	2	0.4846	0.8750	0.5309	0.7440
	HAEMANGIOSARCOMA	1	0	1	0	0.7772	1.0000	0.7686	1.0000
	HEPATOCELLULAR ADENO	8	7	9	5	0.8694	0.7132	0.5390	0.9186
	HEPATOCELLULAR CARCI	3	2	1	0	0.9830	0.8196	0.9490	1.0000
LN INGUINAL	HAEMANGIOSARCOMA	0	0	0	1	0.2751	.	.	0.5361
LN MESENTERIC	HAEMANGIOMA	1	1	1	0	0.8522	0.7472	0.7686	1.0000

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=60	8 mg Low N=60	25 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LUNGS + BRONCHI	BRONCHIOLOALV ADENOM	13	16	20	17	0.5115	0.3529	0.1601	0.4528
	BRONCHIOLOALV ADENOC	3	8	9	7	0.4016	0.1128	0.0810	0.2345
	BRONCH_ADENO+ADENOCA	15	24	27	24	0.3824	0.0779	0.0341	0.1789
PANCREAS	ISLET CELL ADENOMA	0	1	1	3	0.0584	0.4944	0.5161	0.1499
PAROTID S.G.	ADENOMA	0	0	1	0	0.5266	.	0.5161	.
PENIS/PREPUCE	CARCINOMA - ACCESSOR	0	1	0	0	0.7619	0.5000	.	.
PINNAE	HAEMANGIOSARCOMA	0	0	0	1	0.2713	.	.	0.5312
PITUITARY	ADENOMA, PARS DISTA	1	1	0	0	0.9437	0.7472	1.0000	1.0000
PREPUTIAL GLAND	SQUAMOUS CELL PAPILL	0	0	0	1	0.2713	.	.	0.5312
SEMINAL VESICLE	ADENOCARCINOMA	0	0	0	1	0.2713	.	.	0.5312
	ADENOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
SKELETAL MUSCLE	FIBROSARCOMA	0	1	0	0	0.7606	0.4944	.	.
	HAEMANGIOSARCOMA	0	0	0	2	0.0746	.	.	0.2848
SKIN	FIBROSARCOMA	0	1	1	0	0.6543	0.4944	0.5161	.
	HAEMANGIOMA	0	0	0	1	0.2751	.	.	0.5361
	MYXOMA	0	0	0	1	0.2713	.	.	0.5312
	SEBACEOUS CELL ADENO	1	0	0	0	1.0000	1.0000	1.0000	1.0000
SPLEEN	HAEMANGIOMA	0	0	0	1	0.2751	.	.	0.5361
	HAEMANGIOSARCOMA	1	0	1	2	0.2031	1.0000	0.7686	0.5546
STOMACH	ADENOMA	0	0	1	0	0.5266	.	0.5161	.
	SQUAMOUS CELL CARCIN	0	0	1	0	0.5266	.	0.5161	.
	SQUAMOUS CELL PAPILL	1	0	0	0	1.0000	1.0000	1.0000	1.0000
TAIL	HAEMANGIOSARCOMA	0	0	0	1	0.2713	.	.	0.5312
	OSTEOSARCOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
TESTES	HAEMANGIOMA	0	1	0	0	0.7606	0.4944	.	.
	INTERSTITIAL (LEYDIG	4	6	4	6	0.4074	0.3695	0.6788	0.4527
TONGUE	SQUAMOUS CELL CARCIN	0	0	0	1	0.2713	.	.	0.5312
WHOLE_BODY	HAEMANG+HAEMANG_SARC	6	3	6	7	0.3211	0.9161	0.6800	0.6259
	LAEUKEMIAS	1	1	0	1	0.5734	0.7528	1.0000	0.7874
	LYMPHOMAS	11	4	7	0	0.9998	0.9861	0.9190	1.0000

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=60	8 mg Low N=60	25 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ABDOMEN	LEIOMYOSARCOMA	0	0	0	1	0.2360	.	.	0.4524
ADIPOSE TISSUE	MESOVARIAN LEIOMYOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
ADRENALS	CORTICAL ADENOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	PHAEOCHROMOCYTOMA	1	0	0	1	0.4175	1.0000	1.0000	0.7031
	SUBCAPSULAR CELL ADE	1	0	1	1	0.3673	1.0000	0.7168	0.7031
ALL_BONES	CHONDROM+OSTEOSAR+OS	0	1	1	2	0.0990	0.4524	0.4651	0.2017
BONE	OSTEOMA	0	0	1	1	0.1726	.	0.4651	0.4524
BRAIN	MENINGIOMA	0	0	0	1	0.2360	.	.	0.4524
	MENINGIOMA_BEN+MALIG	0	0	0	2	0.0546	.	.	0.2017
CAECUM	LEIOMYOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
COLON	POLYPOPID ADENOMA	0	1	0	0	0.7143	0.4458	.	.
DUODENUM	OSTEOSARCOMA	0	1	0	0	0.7160	0.4524	.	.
FEMUR INC. JOIN	OSTEOMA	0	0	0	1	0.2360	.	.	0.4524
H-POIETIC TUMOU	HISTIOCYTIC SARCOMA	3	7	1	2	0.8308	0.1075	0.9199	0.7466
	LYMPHOMA	6	11	11	22	<0.001*	0.0918	0.1012	<0.001*
	MYELOID CELL LEUKAEM	2	0	0	0	1.0000	1.0000	1.0000	1.0000
HARDERIAN GLAND	ADENOCARCINOMA	0	1	0	0	0.7143	0.4458	.	.
	ADENOMA	5	5	2	4	0.5420	0.5060	0.9157	0.6403
LIVER	HAEMANGIOMA	0	0	1	0	0.4845	.	0.4651	.
	HEPATOCELLULAR ADENO	0	0	0	1	0.2360	.	.	0.4524
LUNGS + BRONCHI	BRONCHIOLOALVEOLAR A	12	7	7	10	0.3228	0.8889	0.8889	0.5876
		5	3	3	1	0.9255	0.7979	0.8180	0.9772
MAMMARY	ADEN+ADENOCARCI+FIBR	1	1	3	3	0.1283	0.7031	0.2571	0.2571
	MAMMARY ADENOCARCINO	1	1	2	3	0.1112	0.7031	0.4471	0.2571
	MAMMARY FIBROADENOMA	0	0	1	0	0.4845	.	0.4651	.
OESOPHAGUS	SQUAMOUS CELL CARCIN	0	0	1	0	0.4845	.	0.4651	.
OVARIES	CHORIOCARCINOMA	0	0	1	0	0.4845	.	0.4651	.
	CYSTADENOMA	2	4	0	1	0.8379	0.2515	1.0000	0.8407
	GRANULOSA CELL TUMOU	1	0	0	1	0.4175	1.0000	1.0000	0.7031
	LUTEOMA	2	1	3	4	0.0886	0.8407	0.4332	0.2515
	MESOVARIAN LEIOMYOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	SERTOLIFORM TUBULAR	0	0	0	2	0.0546	.	.	0.2017
PANCREAS	ISLET CELL ADENOMA	1	1	2	0	0.7641	0.7031	0.4564	1.0000

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Mice

Organ Name	Tumor Name	0 mg Cont N=60	8 mg Low N=60	25 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
PAROTID S.G.	ADENOMA	0	0	1	0	0.4877	.	0.4713	.
PINNAE	HAEMANGIOMA	0	1	0	0	0.7160	0.4524	.	.
PITUITARY	ADENOMA, PARS DISTA	7	2	6	0	0.9874	0.9647	0.6290	1.0000
	ADENOMA, PARS INTERM	0	0	0	1	0.2360	.	.	0.4524
SKELETAL MUSCLE	OSTEOSARCOMA	0	0	0	1	0.2360	.	.	0.4524
SKIN	CHONDROMA	0	0	1	0	0.4845	.	0.4651	.
	FIBROSARCOMA	2	0	1	0	0.8654	1.0000	0.8517	1.0000
	SARCOMA NOS	1	0	0	1	0.4175	1.0000	1.0000	0.7031
	TRICHOEPITHELIOMA	0	1	1	1	0.2648	0.4458	0.4651	0.4524
SPLEEN	HAEMANGIOMA	0	1	0	0	0.7143	0.4458	.	.
	HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
STOMACH	ADENOMA	1	0	1	0	0.7358	1.0000	0.7168	1.0000
THYROIDS	FOLLICULAR CELL ADEN	2	0	0	0	1.0000	1.0000	1.0000	1.0000
UTERINE CERVIX	ADENOMA	0	1	0	0	0.7143	0.4458	.	.
	BASAL CELL CARCINOMA	0	0	0	1	0.2360	.	.	0.4524
	ENDOMETRIAL POLYP	1	0	1	1	0.3673	1.0000	0.7168	0.7031
	FIBROMA	0	0	1	0	0.4845	.	0.4651	.
	LEIOMYOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000
UTERUS	DECIDUOMA	0	0	1	0	0.4845	.	0.4651	.
	ENDOMETRIAL POLYP	2	1	5	3	0.2189	0.8407	0.1631	0.4091
	ENDOMETRIAL STROMAL	0	0	1	0	0.4845	.	0.4651	.
	FIBROMA	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	HAEMANGIOMA	1	5	1	0	0.9496	0.0636	0.7168	1.0000
	LEIOMYOMA	3	1	5	3	0.3087	0.9112	0.2937	0.5666
	LEIOMYOMAS+LEIOMYOSA	3	1	7	4	0.2050	0.9112	0.1143	0.4072
	LEIOMYOSARCOMA	0	0	2	1	0.1879	.	0.2134	0.4588
	MALIGNANT SCHWANNOMA	1	1	0	0	0.9196	0.6959	1.0000	1.0000
VAGINA	GRANULAR CELL TUMOUR	0	0	0	1	0.2360	.	.	0.4524
	HAEMANGIOMA	0	0	0	1	0.2360	.	.	0.4524
WHOLE_BODY	HAEMANG+HAEMANG_SARC	2	7	2	1	0.9114	0.0461	0.6372	0.8407
	LAEUKEMIAS	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	LYMPHOMAS	6	11	11	22	<0.001*	0.0918	0.1012	<0.001*

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

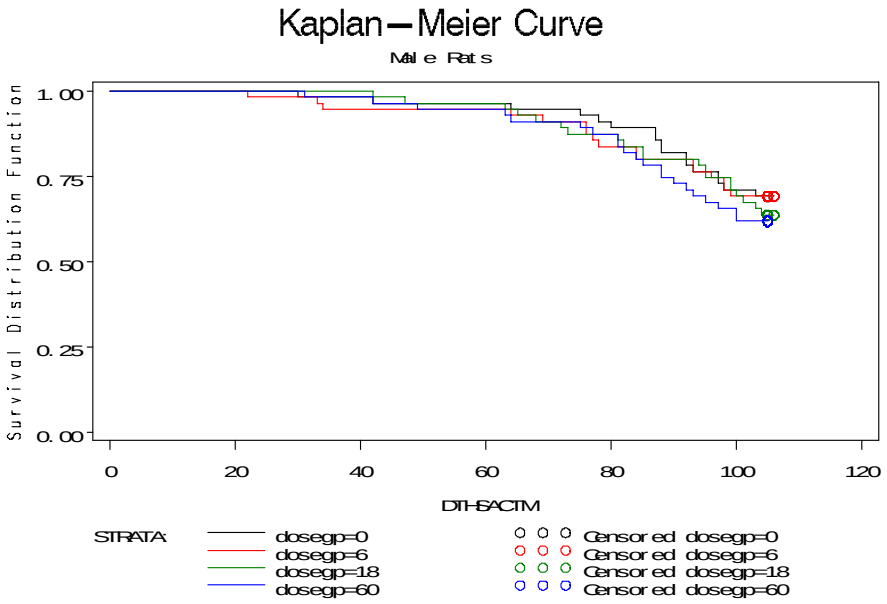


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

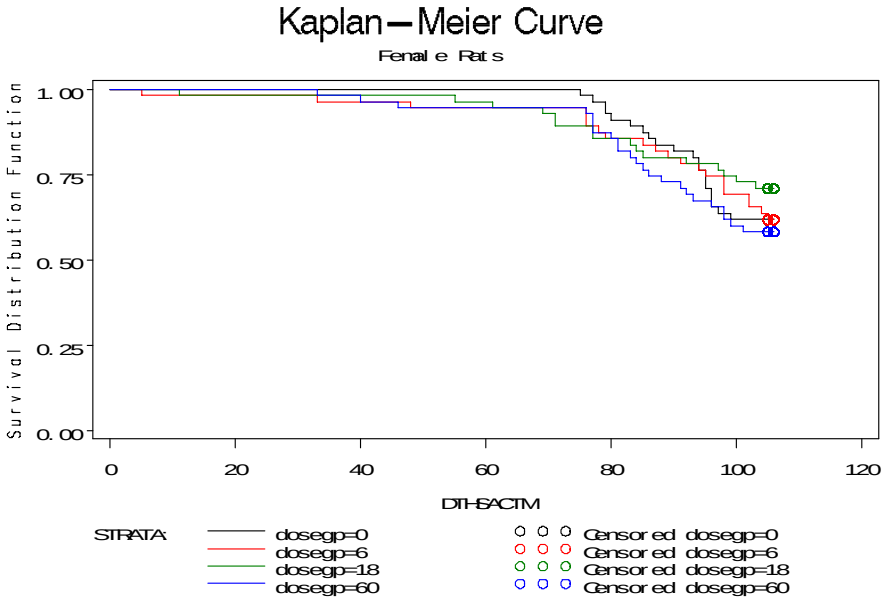


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

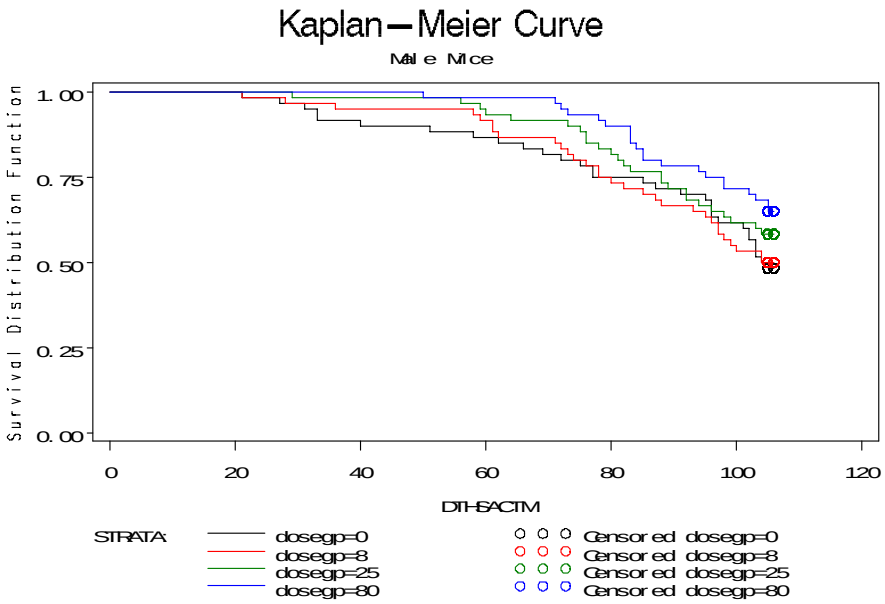
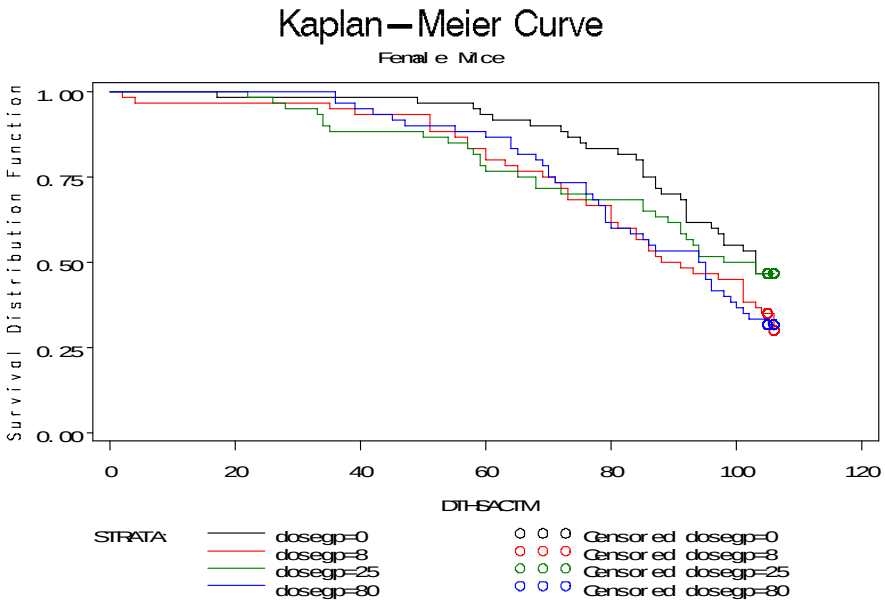


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



References

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
3. *Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rorent Carcinogenicity Statues of Pharmaceuticals (Draft Guidance).* U.S. Department of Health and Human Services, Food and Drug Administation, Center for Drug Evaluation and Research (CDER), May 2001.
4. Haseman, J, "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339, 1983.
5. Lin K.K. and Rahman M.A.," Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics,* 8(1), 1-15, 1998.
6. Mantel N. (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports*, **50**, 163-170.
7. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J.Wahrendorf, "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva,* 311-426, 1980.
8. Tarone RE, "Test for trend in life table analysis", *Biometrika* 1975, 62: 679-82.

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

/s/

ATIAR MOHAMMAD A RAHMAN
02/18/2011

KARL K LIN
02/21/2011
Concur with review

STATISTICS FILING CHECKLIST FOR NDA/BLA

NDA Number: 201280 **Applicant:** Boehringer Ingelheim **Stamp Date: 7/2/2010**

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.)	✓			Clinical overview and reports for individual studies are available
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			For efficacy
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 whose results are used to support the efficacy in the sponsor proposed labeling.

Study	Treatments	Duration	Centers (countries)	n	HbA1c Diff (95% CI)
1218-15	Lina + Pio PBO + Pio	24-WK	43 (7)	252 128	-0.51 (-0.72. -0.30)*
1218-16	Lina PBO	24-WK	66 (11)	333 163	-0.69 (-0.85, -0.53)*
1218-17	Lina + Met PBO + Met	24-WK	82 (10)	513 175	-0.64 (-0.78, -0.50)*
1218-18	Lina + Met + SU PBO+ Met + SU	24-WK	100 (11)	778 262	-0.62 (-0.73, -0.50)*
1218-20	Lina + Met Glimepiride + Met	52-WK	209 (16)	766 761	0.22 (0.13, 0.31)^
1218-35	Lina + SU PBO + SU	18-WK	45 (7)	158 82	-0.47 (-0.70, -0.24)
1218-50	Lina PBO (in Met-intolerant patients)	18-WK	53 (7)	147 73	-0.57 (-0.86, 0.29)

Lina=linagliptin, Pio=pioglitazone, PBO=placebo, Met=metformin, SU=sulfonylurea
* Studies 1218-15, -16, -17, and -18 were pivotal double-blind placebo-controlled trials.
^ NI margin 0.35%

Wei Liu **08/9/2010**

Reviewing Statistician Date

Supervisor/Team Leader Date

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

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

/s/

WEI LIU
08/09/2010

JON T SAHLROOT
08/09/2010