CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	206111
Supplement #:	
Drug Name:	Synjardy (Empagliflozin and Metformin Tablets)
Indication(s):	To improve glycemic control in adults with type 2 diabetes mellitus
Applicant:	Boehringer Ingelheim
Date(s):	Stamp date: August, 2014
	Primary review due date: April 15, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Shuxian Sinks, PhD
Concurring Reviewers:	Mark Rothmann, PhD, Team Leader
	Thomas Permutt, PhD, Division Director
Medical Division:	Division of Metabolic and Endocrine Products
Clinical Team:	William Chong, M.D., Diabetes Team Leader
Project Manager:	Michael White

Keywords: NDA review, clinical studies, non-inferiority, sensitivity analysis, labelling

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Boehringer Ingelheim proposed Synjardy (Empagliflozin/Metformin combination) for the improvement of glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4) The primary endpoint of change in HbA1c was met in each of the randomized, controlled Phase 3 efficacy trials that were included in this submission. Based on the prespecified analysis of the primary study endpoint:

- Empagliflozin 25mg showed non-inferiority to glimepiride in terms of reduction in HbA1c when added on background therapy of metformin.
- Empagliflozin 25mg and Empagliflozin 10mg achieved statistically significance reduction in HbA1c compared to placebo when added on insulin regimen along or with Metformin.
- Empagliflozin 12.5mg was non-inferior to empagliflozin 25mg; Empagliflozin 5mg was non-inferior to empagliflozin 10mg.

Metformin dosage was fixed at patient-level and used as background therapy in the clinical trials. My review supports the empagliflozin is effective therapy for treatment for patients with T2DM in metformin population. (b) (4)

The amount of missing data ranges from 7.3% to 16.7% at week 104 across the reviewed studies. However, the sponsor imputed missing data based on the observed cases where patients were on-treatment using last observation carried forward (LOCF) method. (b) (4) The primary analysis population should include both on-treatment and off-treatment measurements. Also, LOCF is no longer recommended by the division for handling missing data.

1.2 Brief Overview of Clinical Studies

This review focused on efficacy data from 3 pivotal trials: 1245.28 *(met)*, 1245.49 *(insulin+/-met)*, 1276.10 *(met)*, which were double-blind, randomized, controlled studies to evaluate the efficacy of oral administration of empagliflozin (10mg or 25 mg) with add-on therapy metformin among patients with T2DM.

1.3 Statistical Issues and Findings

Based on my statistical review, both Empagliflozin 25mg and Empagliflozin 10mg improved control on the primary study endpoint compared with placebo. The upper limit of the 97.5% confidence intervals for the difference in mean change between the experimental and control arms were below the specified non-inferiority margin, non-inferiority conclusions on

empagliflozin 25 vs Glimepiride/ Empagliflozin 5mg bid and 12.5mg bid versus reference therapy with empagliflozin 10mg qd and 25 mg qd were established.

The key secondary endpoints varied and were ranked in different orders for each clinical study. The sponsor did not thoroughly explain the rationale of why the secondary endpoints needed to be studied. The statistical significant of each secondary was achieved after adjusting multiplicity. However, the indication of clinical importance of the difference is due to clinical reviewer.

The extent of missing data varied across studies and timing of the primary endpoint landmark visit. For study 1245.28, the landmark for the primary endpoint was at week 104 and the percent of missing data was about 16% for both arms. For study 1245.49, the primary endpoint was at week 18 and the percent of missing data was around 9% to 10% (Empa 25mg, Empa 10mg, and placebo). For study 1276.10, the primary endpoint was at week 16 and percentage of missing data in treatment group was higher than placebo group (Empa 12.5mg bid :7.3%, Empa 25mg qd : 6.4%, Empa 5mg bid: 7.8%, Empa 10mg qd: 8.2%, placebo: 4.7%).

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Empagliflozin and metformin hydrochloride fixed dose combination tablets are indicated for the use of improving glycemic control in adults with type 2 diabetes mellitus [redacted] (b) (4)

2.1.2 History of Drug Development

The clinical development of empagliflozin to improve glycemic control in adults with T2DM started in January 2007. The clinical program established the initial application of empagliflozin as monotherapy, which comprised 30 Phase I trials, 5 Phase II trials, and 13 Phase IIb/III trials. Empagliflozin (Jardiance) was approved by FDA on August 1, 2014.

Boehringer Ingelheim submitted the NDA 206111 on August 4, 2014 to provide information in supporting the bridge of the efficacy and safety obtained with the free combination use of empagliflozin and metformin in Phase IIb/III clinical trials and also the information to support the bridging of empagliflozin administered once daily as compared to twice daily.

2.1.3 Specific Studies Reviewed

This review focuses on 3 new studies which were not submitted in previous Empagliflozin submission. Summary of the trial designs were given in Table 1.

Table 1: List of all studies included in analysis

Trial	Phase and	Treatment	Follow-	# of Subjects per	Study

No.	Design	Period (weeks)	up Period (weeks)	Arm	Population
1245.28	Phase 3, stratified by screening HbA1c level, renal eGFR and region	104	1	Empa+Met: 765 patients; Glime+Met: 780 patients	T2DM and insufficient glycemic control
1245.49	Phase 3, insulin along or with metformin	52	4	Empa 10 mg insulin+/- met: 186 patients; Empa 25 mg insulin +/- met: 189 patient; Placebo+ insulin +/- met: 188 patients	T2DM inadequately controlled on Multiple daily injections
1276.10	Phase 2b, stratified by HbA1c screening level, screening renal function eGFR, and region	16	1	Empa 12 mg bid +Met: 215 patients; Empa 25 mg qd + Met: 214 patients; Empa 5mg bid+ Met: 215 patients; Empa 10 mg qd+ Met: 214 patients; Placeb+Met: 107 patients	T2DM and insufficient glycemic control

2.2 Data Sources

The data and the final study report were submitted electronically as an eCTD submission. The submission was archived at the following link: \\CDSESUB1\evsprod\NDA206111\206111.enx >. The information needed for this review was obtained from Module 1 FDA regional information, Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Report. All tables and figures in this review were created by this reviewer unless noted otherwise.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

All required documents necessary for conducting a statistical review were submitted. The reviewer requested software code from the sponsor to validate the analyses. The datasets for the three clinical trials were found to be in good organization and were provided as an ,xpt files. The analysis datasets included both derived and enriched data (such as formatted variables, derived endpoint, data imputation information, etc.) Across trials the variables for the primary analysis were consistently named. I was able to produce the results on the primary endpoints and secondary endpoints presented in the individual Clinical Study Report.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary efficacy endpoint was the change from baseline in HbA1c at a specified time point in all 3 clinical trials. For study 1245.28, the primary efficacy endpoints were at week 52 and 104; for study 1245.49, the primary efficacy endpoint was at week 18; for study 1276.10, the primary efficacy endpoint was at week 16.

All key secondary efficacy endpoint in 2 Phase III studies were summarized in Table 2, which were tested in hierarchical order.

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Table 2 Summary of Key Secondary Endpoints for Reviewed Phase III studies

Hierarchical Testing Order	Study 1245.28	Study 1245.49
1	Change from baseline in Body weight at 52 and 104 weeks	Change from baseline in insulin at 52 weeks
2	Occurrence of Confirmed symptomatic hypoglycaemic events during 52 and 104 weeks	Change from baseline in body weight at 52 weeks
3	Change in blood pressure (SBP and DBP) from baseline at 52 and 104 weeks	Change from baseline in HbA1c at 52 weeks

The secondary efficacy endpoints for study 1276.10 included: the change from baseline in fasting plasma glucose (FPG) at week 16; the change from baseline in HbA1c over time.

3.2.2 Statistical Methodologies

Analysis Method

The **sponsor** used analysis of covariance (ANCOVA) model to conduct the primary analysis of the HbA1c change from baseline. The model included baseline HbA1c as covariate, treatment and stratification factors (eg. renal function, region, background antidiabetic therapy) as fixed effect. Missing data were imputed by using last observation carried forward (LOCF) method. For the key secondary endpoints analysis, ANCOVA model was performed for the change of each key secondary endpoint from baseline, where the model was similar to the model in primary analysis.

Hypothesis Testing

Study 1245.28
Ho1: Empagliflozin 25mg is inferior to Glimepiride in change of HbA1c from baseline
Ha1: Empagliflozin 25mg is not inferior to Glimepiride in change of HbA1c from baseline
If non-inferiority for HbA1c was established, superiority on the key secondary efficacy endpoints will be then tested.

Study 1245.49
Ho1: No difference in change of HbA1c between Empagliflozin10 mg and placebo
Ha1: A difference in change of HbA1c between Empagliflozin 10 mg and placebo
Ho2: No difference in change of HbA1c between Empagliflozin 25 mg and placebo
Ha2: A difference in change of HbA1c between Empagliflozin 25 mg and placebo

Each of the hypotheses will be tested at 2.5% (two-sided). Subsequent tests were done only for exploratory purpose at 5% level. All other hypotheses on secondary endpoint were specified to maintain the family wise error at each side of 2.5% level.

Study 1276.10
Ho1: Mean Change from baseline in HbA1c after 16 weeks of treatment with Empagliflozin 5 mg twice daily is greater than that of treatment with Empagliflozin 10 mg once daily by 0.35%
Ha1: Mean change from baseline in HbA1c after 16 weeks of treatment with Empagliflozin 5 mg twice daily is less than that of treatment with Empagliflozin 10 mg once daily by 0.35%

And

Ho2: Mean Change from baseline in HbA1c after 16 weeks of treatment with Empagliflozin 12.5 mg twice daily is greater than that of treatment with Empagliflozin 25 mg once daily by 0.35%
Ha2: Mean change from baseline in HbA1c after 16 weeks of treatment with Empagliflozin 12.5 mg twice daily is less than that of treatment with Empagliflozin 25 mg once daily by 0.35%

Non-inferiority margin was chosen based on the analysis results of study 1245.10, where the overall treatment effects of Empagliflozin 25mg and Empagliflozin 10mg were around -0.70%. Hochberg procedure was applied to control the family-wise type I error at 2.5% (one-sided). Superiority tests of Empagliflozin over placebo were conducted to demonstrate assay sensitivity against placebo at 5% level (two-sided).

Analysis Population

All primary analyses of efficacy endpoints were conducted on full analysis set (FAS) unless otherwise indicated. The FAS included all randomized subjects and treated patients who had a baseline HbA1c value. Sensitivity analyses of the primary endpoint provided by the sponsor were performed on per-protocol sets with specified endpoints and completer sets to evaluate the influence of important protocol violations and premature discontinuations. The per-protocol set compromised of all patients in the FAS without important protocol violations leading to exclusion prior to the endpoint. The completer set excluded patients who prematurely discontinued prior to the endpoint and who completed required the minimum treatment duration.

Missing Data and Sensitivity Analysis

The sponsor used last observation carried forward (LOCF) approach for the primary analysis to handle the missing data due to early discontinuation of study medication. Missing data were imputed up to the planned visit to be reached by all randomized patients. Missing values within a course of measurements on treatment were interpolated based on the last observed value before the missing visit and the first observed value after the missing visit. Baseline values were carried forward if no post-randomization were observed. All values observed after rescue medication were excluded and imputed using the LOCF method.

This reviewer notes that the LOCF method is no longer recommended for missing data imputation. More details are provided in the 2010 report on missing data by the National Academy of Sciences (NAS), the prevention and treatment of missing data in clinical trials. Additionally, the primary analysis ignored actual observations after discontinuation of protocol therapy.

Sensitivity analyses reported by the sponsor for the primary efficacy endpoint includes 1) the analyses based on observed cases including values on rescue medication (OC-IR), where missing data were not imputed and all values observed after a patient started rescue medication were included, 2) the analyses based on observed cases (OC), where missing data were imputed using multiple imputation , 3) the analyses based on FAS (OC) and FAS (OC-IR) using MMRM approach, where the fitted model underlie the assumption of missing at random. Results of sensitivity analyses were similar to that of the primary analysis proposed by sponsor.

This reviewer notes that the sponsor's sensitivity analysis 3) creates more missing data and thereby does not study the limitations of the data or of the primary analysis.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

According to **the sponsor**, patients who discontinued study medication before the end of treatment were requested to attend scheduled visit continually by the end of study.

Of **study 1245.28**, 1549 patients were randomized; 4 patients of Empagliflozin group did not have baseline assessment of HbA1c, and 1545 subjects comprised the full analysis set. Patient disposition for study 1245.28 was presented in details in Table 3. At 104 weeks, 1055 (68.3%) patients were on study medication: 545 (71.2%) patients in Empagliflozin 25 mg group, 521 (65.4%) patients in the Glimepiride group. A total of 267 patients prematurely discontinued from study medication during the 104 weeks of treatment, where 125 (16.3 %) patients were from Empagliflozin group and 142 (18.2%) patients were from the Glimepiride group. Total numbers of patient refusal to take the study medication due to adverse event (AE) versus not due to AE were similar: 35 patients vs 38 patients in Empagliflozin 25mg group, 34 patients vs 31 patients in Glimepiride group.

Of **study 1245.49**, 566 patients were randomized; 3 patients were randomized but not treated, therefore, the full analysis set consisted of 563 patients. At 52 weeks, 457 (84.4%) patients were still on study medication and 488 (86.7%) patients were still in the trial. As presented in Table 4, the proportion of patients discontinued from study medication in empagliflozin 25 mg was lower than that of patients in empagliflozin 10mg group. 28 (5%) patients discontinued study medication due to adverse event (Placebo: 9 patients, Empagliflozin 10mg: 10 patients, Empagliflozin 25: 9 patients).

Of **Study 1276.10**, 983 patients were randomized and treated, and 93.2% completed 16 weeks of treatment and 67 (6.8%) patients discontinued study medication. The full analysis set consisted of all 983 randomized patients regardless of early withdrawal. More patients in Empagliflozin groups discontinued from study medication than patients from placebo group. Empagliflozin 10 mg group had the highest rate of discontinuation study medication due to adverse event, 13 patients out of total 28 patients in the trial. Only one patient, in placebo group, discontinued the study medication due to lack of efficacy.

Table 3 Patient Disposition for Study 1245.28 –at 104 weeks

	Empagliflozin 25mg	**Glimepiride**
	N (%)	N (%)
Treated	765 (100)	780 (100)
Still on study medication	545 (71.2)	510 (65.4)
Did not continue to extension period	95 (12.4)	128 (16.4)
Prematurely discontinued study medication		
AE-Unexpected worsening of pre-existing disease	2 (0.3)	4 (0.5)
AE-Unexpected worsening of disease under study	3 (0.4)	8 (1.0)
Other AE	33 (4.3)	22 (2.8)
Lack of efficacy	3 (0.4)	3 (0.4)
Non-complaint with protocol	6 (0.8)	13 (1.7)
Lost to follow-up	16 (2.1)	15 (1.9)
Withdrawal by subject	37 (4.8)	31 (4.0)
Other	25 (3.3)	46 (5.9)

Table 4 Patient Disposition for Study 1245.49

	Empagliflozin 10 mg	**Empagliflozin 25 mg**	**Placebo**
	N (%)	N (%)	N (%)
Treated	187 (100)	189 (100)	188 (100)

	Empagliflozin 10 mg		Empagliflozin 25 mg		Placebo	
	N	(%)	N	(%)	N	(%)
Not prematurely discontinued (study medication)	155	(83.3)	163	(86.2)	157	(83.5)
Prematurely discontinued study medication						
AE- Unexpected worsening of pre-existing disease	1	(0.5)	0		0	
AE- Unexpected worsening of disease under study	0		0		1	(0.5)
Other AE	9	(4.8)	9	(4.8)	8	(4.3)
Non-complaint with protocol	4	(2.2)	4	(2.1)	7	(3.7)
Lost to follow-up	5	(2.7)	2	(1.1)	2	(1.1)
Withdrawal by subject	9	(4.8)	8	(4.2)	9	(4.8)
Other	3	(1.6)	3	(1.6)	4	(2.1)

Table 5 Patient Disposition for Study 1276.10

	Empa 5mg		Empa 10 mg		Empa 12.5 mg		Empa 25 mg		Placebo tablet	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Treated	219	(100)	220	(100)	219	(100)	218	(100)	107	(100)
Not prematurely discontinued study medication	202	(92.2)	201	(91.4)	205	(93.6)	205	(94.0)	103	(96.3)
Prematurely discontinued study medication										
AE-Unexpected worsening of disease under study	0		1	(0.5)	1	(0.5)	1	(0.5)	0	
Other AE	4	(1.8)	12	(5.5)	4	(1.8)	4	(1.8)	1	(0.9)
Lack of efficacy	0		0		0		0		1	(0.9)
Non-complaint with protocol	3	(1.4)	2	(0.9)	1	(0.5)	0		1	(0.9)
Lost to follow-up	4	(1.8)	3	(1.4)	1	(0.5)	1	(0.5)	0	
Withdrawal by subject	4	(1.8)	1	(0.5)	3	(1.4)	6	(2.8)	1	(0.9)

Demographic and Baseline Characteristics

As presented in tables, the key demographics and baseline characteristics were fairly balanced across the randomized treatment groups for the reviewed studies.

Of study 1245.28, there were slightly more male patients then female patients. Majority of patients were White (65.9%) and about third of patients were Asian. The average age of all

patients was 55.9 years (SD 10.4 years) and more than 75% of patients were below 65 years old. 41% of patients had normal renal function at baseline assessment, and over 56% patients had mild renal function. The mean baseline HbA1c level was at 7.9% (SD 0.84%) and 43% patients had been diagnosed T2DM for more than 1 year but less than 5 years.

Table 6 Baseline Demographics for Study 1245.28

	Empagliflozin 25 mg	Glimepiride	Total
Age			
Mean (SD)	56.2 (10.3)	55.7 (10.44)	55.9 (10.37)
Age, N (%)			
50 to <65	395 (51.6)	417 (53.5)	815 (52.6)
65 to <75	145 (19.0)	125 (16.0)	270 (17.4)
<50	197 (25.8)	212 (27.2)	410 (26.5)
>=75	28 (3.7)	26 (3.3)	54 (3.5)
Ethnic, N (%)			
Hispanic	153 (20.0)	159 (20.4)	312 (20.1)
Not Hispanic	612 (80.0)	621 (79.6)	1237 (79.9)
Race, N (%)			
Asian	254 (33.2)	253 (32.4)	508 (32.8)
Black	12 (1.6)	8 (1.0)	20 (1.3)
Native Hawaiian	1 (0.1)	0 (0.0)	1 (0.1)
White	498 (65.1)	519 (66.5)	1020 (65.8)
Region, N (%)			
Asia	215 (28.1)	219 (28.1)	435 (28.1)
Europe	317 (41.4)	322 (41.3)	641 (41.4)
Latin America	136 (17.8)	140 (17.9)	276 (17.8)
North America	97 (12.7)	99 (12.7)	197 (12.7)
Sex, N (%)			
Female	333 (43.5)	359 (46.0)	694 (44.8)
Male	432 (56.5)	421 (54.0)	855 (55.2)

Table 7 Baseline Characteristics for Study 1245.28

	Empagliflozin 25 mg	Glimepiride	Total
FPG			
Mean (SD)	150 (31.96)	149.8 (35.7)	149.9 (33.9)

	Empagliflozin 25 mg	Glimepiride	Total
DBP			
Mean (SD)	79.5 (9.59)	79.4 (9.24)	79.5 (9.41)
eGFR, N (%)			
30 to <60(moderate)	13 (1.7)	22 (2.8)	35 (2.3)
60 to <90(mild)	439 (57.4)	440 (56.4)	879 (56.9)
>=90(normal)	313 (40.9)	318 (40.8)	631 (40.8)
HbA1c (%)			
Mean (SD)	7.9 (0.81)	7.9 (0.86)	7.9 (0.84)
HbA1c (%), N (%)			
<8.5	584 (76.3)	589 (75.5)	1173 (75.9)
>=8.5	181 (23.7)	191 (24.5)	372 (24.1)
BMI			
Mean (SD)	29.9 (5.28)	30.3 (5.3)	30.1 (5.29)
BMI, N (%)			
25 to <30	284 (37.1)	303 (38.8)	587 (38.0)
30 to <35	214 (28.0)	220 (28.2)	434 (28.1)
<25	131 (17.1)	112 (14.4)	243 (15.7)
>=35	136 (17.8)	145 (18.6)	281 (18.2)
SBP			
Mean (SD)	133.4 (15.92)	133.5 (15.98)	133.5 (15.95)

Of **study 1245.49**, there were more female patients than male patients overall (54.4% vs 45.6%). The average age of patients in the study was 56.7 (SD 9.46) years old and over half percent of patients were in the range from 50 to 65 years old. Patients were from Europe (55.5 %), Latin America (31.6%), and North America (12.9 %). A large majority of patients were white (94.3%) in the study. 60.4% patients had mild renal function at baseline assessment before taking the study medication, and 34.6 % patients had normal renal function. The average baseline HbA1c level of patients was 8.3% (SD 0.73).

Table 8 Baseline Demographics for Study 1245.49

	Empagliflozin 10 mg	Empagliflozin 25 mg	Placebo	Total
Age				
Mean (SD)	56.7 (8.68)	58 (9.39)	55.3 (10.1)	56.7 (9.46)
Age, N (%)				
50 to <65	113 (60.8)	108 (57.1)	104 (55.3)	326 (57.6)

	Empagliflozin 10 mg	Empagliflozin 25 mg	Placebo	Total
65 to <75	32 (17.2)	41 (21.7)	35 (18.6)	110 (19.4)
<50	38 (20.4)	33 (17.5)	49 (26.1)	120 (21.2)
>=75	3 (1.6)	7 (3.7)	0 (0.0)	10 (1.8)
Ethnic, N (%)				
Hispanic	65 (34.9)	74 (39.2)	67 (35.6)	207 (36.6)
Non-Hispanic	121 (65.1)	115 (60.8)	121 (64.4)	359 (63.4)
Race, N (%)				
American Indian	3 (1.6)	2 (1.1)	4 (2.1)	9 (1.6)
Asian	0 (0.0)	1 (0.5)	2 (1.1)	3 (0.5)
Black	7 (3.8)	4 (2.1)	8 (4.3)	19 (3.4)
Native Hawaiian	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
White	175 (94.1)	182 (96.3)	174 (92.6)	534 (94.3)
Region, N (%)				
Europe	101 (54.3)	105 (55.6)	106 (56.4)	314 (55.5)
Latin America	59 (31.7)	61 (32.3)	58 (30.9)	179 (31.6)
North America	26 (14.0)	23 (12.2)	24 (12.8)	73 (12.9)
Sex, N (%)				
Female	89 (47.8)	105 (55.6)	113 (60.1)	308 (54.4)
Male	97 (52.2)	84 (44.4)	75 (39.9)	258 (45.6)

Table 9 Baseline Characteristics for Study 1245.49

	Empagliflozin 10 mg	Empagliflozin 25 mg	Placebo	Total
FPG				
Mean (SD)	159.1 (47.94)	150.3 (48.63)	151.6 (45.83)	153.6 (47.56)
DBP				
Mean (SD)	79.5 (8.47)	78.7 (8.49)	78.2 (8.77)	78.8 (8.58)
eGFR, N (%)				
30 to <60 (moderate)	13 (7.0)	7 (3.7)	8 (4.3)	28 (5.0)
60 to <90 (mild)	108 (58.1)	112 (59.3)	120 (63.8)	340 (60.4)
>=90 (normal)	65 (34.9)	70 (37.0)	60 (31.9)	195 (34.6)
HbA1c (%)				
Mean (SD)	8.4 (0.74)	8.3 (0.72)	8.3 (0.72)	8.3 (0.73)
HbA1c (%), N (%)				

	Empagliflozin 10 mg	Empagliflozin 25 mg	Placebo	Total
<8.5	101 (54.3)	112 (59.3)	105 (55.9)	318 (56.5)
>=8.5	85 (45.7)	77 (40.7)	83 (44.1)	245 (43.5)
BMI				
Mean (SD)	34.7 (3.83)	35 (4.04)	34.7 (4.3)	34.8 (4.06)
BMI, N (%)				
25 to <30	6 (3.2)	8 (4.2)	8 (4.3)	22 (3.9)
30 to <35	99 (53.2)	104 (55.0)	108 (57.4)	311 (55.2)
>=35	81 (43.5)	77 (40.7)	72 (38.3)	230 (40.9)
SBP				
Mean (SD)	134.2 (16.4)	132.9 (14.2)	132.6 (15.81)	133.3 (15.48)

Of **study 1276.10**, 54.2% patients were male and 45.8% patients were female. Similar to the other reviewed studies, the mean age of patients in the study was 58.2 (SD 10.4) and more than half of patients ranged from 50 to 65 years old. About 60% patients were enrolled from Europe and 30% patients were enrolled from North America. The majority of patients were white (85.5%) in the study. Asian and black patients were 4.6% and 6.8% correspondingly. The number of patients who had mild was similar (48.9%) to that of patients who had normal renal function at baseline (45.3%). The average baseline HbA1c level of patients was 7.8% (0.79) overall.

Table 10 Baseline Demographics for Study 1276.10

	Empa10 mg qd	Empa 12.5 mg bid	Empa 25 mg qd	Empa 5 mg bid	Placebo tablet	Total
Age						
Mean (SD)	58.4 (10.9)	57.6 (9.9)	58.1 (10.3)	58.9 (10.1)	57.9 (11.2)	58.2 (10.4)
Age, N (%)						
50 to <65	112 (50.9)	118 (53.9)	111 (50.9)	106 (48.4)	54 (50.5)	501 (51.0)
65 to <75	53 (24.1)	52 (23.7)	49 (22.5)	57 (26.0)	25 (23.4)	236 (24.0)
<50	45 (20.5)	44 (20.1)	47 (21.6)	44 (20.1)	23 (21.5)	203 (20.7)
>=75	10 (4.5)	5 (2.3)	11 (5.0)	12 (5.5)	5 (4.7)	43 (4.4)
Ethnic, N (%)						
Hispanic	42 (19.1)	36 (16.4)	43 (19.7)	42 (19.2)	23 (21.5)	186 (18.9)
Non-Hispanic	178 (80.9)	183 (83.6)	175 (80.3)	177 (80.8)	84 (78.5)	797 (81.1)
Race, N (%)						
American	10 (4.5)	6 (2.7)	3 (1.4)	3 (1.4)	4 (3.7)	26 (2.6)

	Empa10 mg qd	Empa 12.5 mg bid	Empa 25 mg qd	Empa 5 mg bid	Placebo tablet	Total
Indian						
Asian	10 (4.5)	16 (7.3)	10 (4.6)	7 (3.2)	2 (1.9)	45 (4.6)
Black	14 (6.4)	17 (7.8)	10 (4.6)	18 (8.2)	8 (7.5)	67 (6.8)
Native Hawaiian	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
White	186 (84.5)	179 (81.7)	194 (89.0)	191 (87.2)	93 (86.9)	843 (85.8)
Region, N (%)						
Europe	134 (60.9)	135 (61.6)	130 (59.6)	131 (59.8)	66 (61.7)	596 (60.6)
Latin America	19 (8.6)	18 (8.2)	17 (7.8)	18 (8.2)	9 (8.4)	81 (8.2)
North America	67 (30.5)	66 (30.1)	71 (32.6)	70 (32.0)	32 (29.9)	306 (31.1)
Sex, N (%)						
Female	109 (49.5)	93 (42.5)	100 (45.9)	96 (43.8)	52 (48.6)	450 (45.8)
Male	111 (50.5)	126 (57.5)	118 (54.1)	123 (56.2)	55 (51.4)	533 (54.2)

Table 11 Baseline Characteristics for Study 1276.10

	Empa 10 mg qd	Empa 12.5 mg bid	Empa 25 mg qd	Empag 5 mg bid	Placebo tablet	Total
FPG						
Mean (SD)	160.8 (40.58)	156.6 (38.6)	157.7 (32.42)	162.5 (40.12)	159.8 (33.91)	159.5 (37.63)
DBP						
Mean (SD)	78.8 (8.44)	78.5 (8.64)	79 (8.28)	78.4 (8.83)	78.3 (9.63)	78.6 (8.66)
eGFR, N (%)						
30 to <60(moderate)	16 (7.3)	11 (5.0)	12 (5.5)	15 (6.8)	3 (2.8)	57 (5.8)
60 to <90(mild)	103 (46.8)	111 (50.7)	102 (46.8)	110 (50.2)	55 (51.4)	481 (48.9)
>=90(normal)	101 (45.9)	97 (44.3)	104 (47.7)	94 (42.9)	49 (45.8)	445 (45.3)
HbA1c (%)						
Mean (SD)	7.8 (0.75)	7.8 (0.79)	7.7 (0.79)	7.8 (0.88)	7.7 (0.72)	7.8 (0.79)
HbA1c (%), N (%)						
<8.5	175 (79.5)	180 (82.2)	176 (80.7)	173 (79.0)	89 (83.2)	793 (80.7)
>=8.5	45 (20.5)	39 (17.8)	42 (19.3)	46 (21.0)	18 (16.8)	190 (19.3)
BMI						
Mean (SD)	31.9 (5.45)	31.5 (5.1)	32.1 (5.28)	31.5 (5.25)	32 (4.95)	31.8 (5.23)

	Empa 10 mg qd	Empa 12.5 mg bid	Empa 25 mg qd	Empag 5 mg bid	Placebo tablet	Total
BMI, N (%)						
25 to <30	66 (30.0)	69 (31.5)	74 (33.9)	75 (34.2)	31 (29.0)	315 (32.0)
30 to <35	71 (32.3)	76 (34.7)	77 (35.3)	68 (31.1)	38 (35.5)	330 (33.6)
<25	23 (10.5)	21 (9.6)	14 (6.4)	22 (10.0)	7 (6.5)	87 (8.9)
>=35	60 (27.3)	53 (24.2)	53 (24.3)	54 (24.7)	31 (29.0)	251 (25.5)
SBP						
Mean (SD)	131.9 (14.6)	130.3 (14.82)	130.9 (15.1)	132.4 (14.37)	131.5 (14.2)	131.4 (14.66)

3.2.4 Results and Conclusions

3.2.4.1 Trial 1245.28

The primary endpoint was the HbA1c (%) from baseline at week 104. The efficacy results for primary endpoints and key secondary endpoints were presented in Table 12.
The adjusted mean change of HbA1c from baseline at 104 week was -0.78% (SE 0.04) for the empagliflozin group and -0.65% (SE 0.04) for the glimepiride group The adjusted difference between treatment groups was -0.13% (SE 0.05; 97.5% CI: -0.23%, 0.02%, $P_{non\text{-}inferiority}$ <0.0001). The sponsor proposed the non-inferiority margin for comparison after 52 weeks and after 104 weeks of the treatment was 0.3%, while no justification on the margin was provided by sponsor. The study was initially included in Empagliflozin (Jardiance) labelling and 0.3% margin was used for the non-inferiority test at week 52. As the confidence interval does not exceed the bound margin 0.3, Empagliflozin was not inferior to Glimepiride.

The key secondary endpoints included change from baseline in body weight, SBP, DBP after 104 weeks of treatment and confirmed hypoglycemia episode at week 104. (b) (4)

Table 12 Summary Analysis Results for Study 1245.28 (Metformin Add-on)

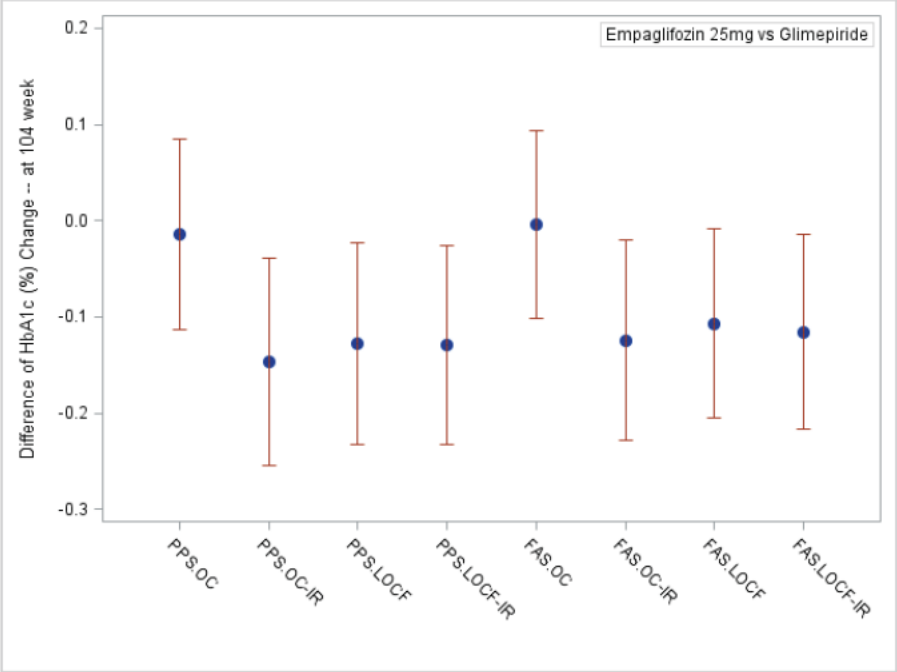
(b) (4)

(b) (4)

Sensitivity analyses of the primary endpoint were performed on full analysis and per-protocol sets using ANCOVA model (see Figure 1). As presented in the following figure, the results were similar to that of MMRM approach. The upper bound of estimated change in HbA1c from baseline at 104 week was below the specified margin and close to zero for each analysis. The confidence interval of estimated primary endpoint covers zero when the analysis was performed on PPS (OC) and FAS (OC). Therefore, **this reviewer** supports that non-inferiority is established

(b) (4)

Figure 1 Summary of Sensitivity Analysis on Change in HbA1c (ANCOVA) for Study 1245.28



3.2.4.2 Trial 1245.49

The results of the primary endpoint and key secondary endpoints were shown in Table 13. The primary endpoint was HbA1c change at week 18 in the study.

(b) (4)

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3.2.4.3 Trial 1276.10

Summary of efficacy results for trial 1276.10 was given in the Table 14 and Table 15.

The primary objective of this Phase IIb trial was to investigate the efficacy of different dosages of empagliflozin (twice daily versus once daily) with combination use of metformin. The primary efficacy endpoint was the change from baseline in HbA1c after 16 weeks of treatment. Comparing twice daily dose (Empa 5mg bid, 12.5mg bid) with once daily dose (, the change in reduction of hbA1c for both group were comparable. The upper limit 97.5% of confidence interval of both comparisons did not exceed the pre-specified non-inferiority margin. The reviewer supports the conclusion that twice administration of empagliflozin is not inferior to once daily administration in terms of reducing HbA1c.

Table 14 Summary Analyses Results for Study 1276.10 on HbA1c Change

	Empa 5mg bid	Empa 10mg qd	Placebo
number of subjects	219	220	107
mean baseline HbA1c (SE)	7.79 (0.79)	7.83 (0.75)	7.69 (0.72)
change from baseline-16 weeks	-0.74 (0.06)	-0.7 (0.06)	-0.28 (0.08)
Comparison vs Empa 10mg qd			
difference (97.5 % CI)	-0.04 (-0.20, 0.14)		
Comparison vs placeb0			
difference (95% CI)	-0.47 (-0.66,-0.27)	-0.43 (-0.63, -0.23)	

	Empa 12.5mg bid	Empa 25mg qd	Placebo
number of subjects	219	218	107
mean baseline HbA1c (SE)	7.78 (0.79)	7.73 (0.79)	7.69 (0.72)
change from baseline-16 weeks	-0.9 (0.06)	-0.78 (0.05)	-0.28 (0.08)
Comparison vs Empa 25mg qd			
difference (97.5% CI)	-0.13 (-0.27, 0.036)		
Comparison vs placebo			
difference (95% CI)	-0.63 (-0.83, -0.42)	-0.5 (-0.69, -0.37)	

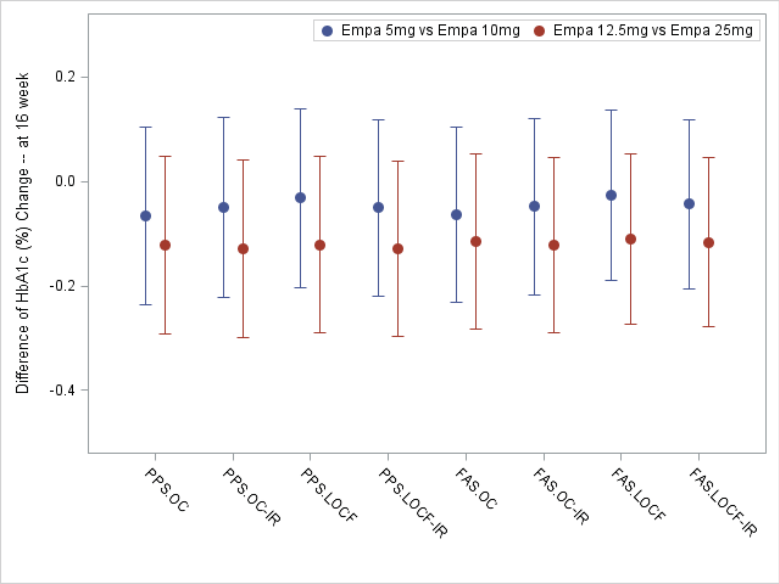
The change from baseline in fasting plasma glucose (PFG) at 16 week was also investigated as key secondary endpoint in the study. The confidence intervals of comparison between twice administrated dose and once daily administrated dose included zero. No statistical significant difference was found between the two administrations on fasting plasma reduction.

Table 15 Summary Analyses Results for Study 1276.10 on FPG change

	Empa 5mg bid	Empa 10mg qd	Placebo
number of subjects	219	220	107
mean baseline FPG (SE)	162.5 (40.1)	160.8 (40.6)	159.8 (33.9)
change from baseline-16 weeks	-24.7 (2.25)	-21.2 (2.02)	-3.76 (4.07)
Comparison vs Empa 10mg qd			
difference (97.5 % CI)	-3.6 (-9.2, 2.1)		
Comparison vs placeb0			
difference (95% CI)	-21 (-30.0, -12.0)	-17.4 (-26.2,-8.6)	
	Empa 12.5mg bid	**Empa 25mg qd**	**Placebo**
number of subjects	218	218	107
mean baseline FPG(SE)	156.6 (38.6)	157.7 (32.4)	159.8 (33.9)
change from baseline-16 weeks	-31.1 (2.07)	-26.2 (2.01)	-3.76 (4.07)
Comparison vs Empa 25mg qd			
difference (97.5% CI)	-4.8 (-10.2, 0.52)		
Comparison vs placebo			
difference (95% CI)	-27.3 (-36.1, -18.5)	-22.5 (-31.3, -13.7)	

As shown in Figure 3, the sensitivity analyses results were similar across different analysis data sets. The results showed the same conclusion on non-inferiority of twice daily administration when compared to once daily administration of empagliflozin.

Figure 3 Summary of Sensitivity Analyses in Change on HbA1c (ANCOVA) for Study 1276.10



4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The factors considered for the subgroup analyses included intrinsic factors (age, race, gender, and region) and disease-related factors (diabetes duration, baseline HbA1c, renal function). Some of these factors may not be included in the individual study due to limited number of subjects in certain subgroup level.

Subgroup analysis on HbA1c (%) was conducted using mixed model used for the primary analysis. Effect estimates were obtained from the model fit to the individual levels that defined the subgroup. Subjects in arms not being tested were excluded from the analysis. The analysis was performed separately for each study. Subgroup analyses were considered as exploratory, which may serve the purpose of hypothesis generating for further testing. Subgroups with number of patients less than 20 were excluded from the report.

Empa+Met compared to Glimepiride (Study 1245.28)

The subgroup analyses results of the efficacy of empagliflozin+metformin compared with glimepiride were consistent across the subgroups. No significant heterogeneity of treatment effect was found across subgroups (gender, race, and region) for comparisons of empagliflozin 25mg +metformin vs glimepiride. For comparison between empagliflozin 25mg and glimepiride, the subgroup analysis on age showed greater treatment effect in younger patients than in older patients. The p-value for the treatment by age interaction is 0.0012. The adjusted mean differences from glimepiride in change of HbA1c from baseline at week 104 were 0.11 (0.06) for patients older than 65 and less than 75 years and 0.043 (0.11) for patients older than 75. In age

group 50 to 65 years old, the treatment effect was -0.05 (0.04). For patients younger than 50 years old, the treatment effect was -0.14 (0.05).

Figure 4 Subgroup Analysis on Change in HbA1c by Region (Study 1245.28)

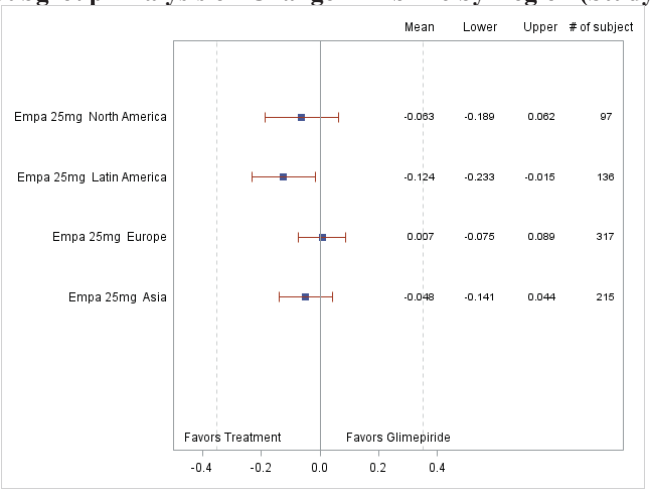


Figure 5 Subgroup Analysis of Change in HbA1c by Gender or by Race (Study 1245.28)

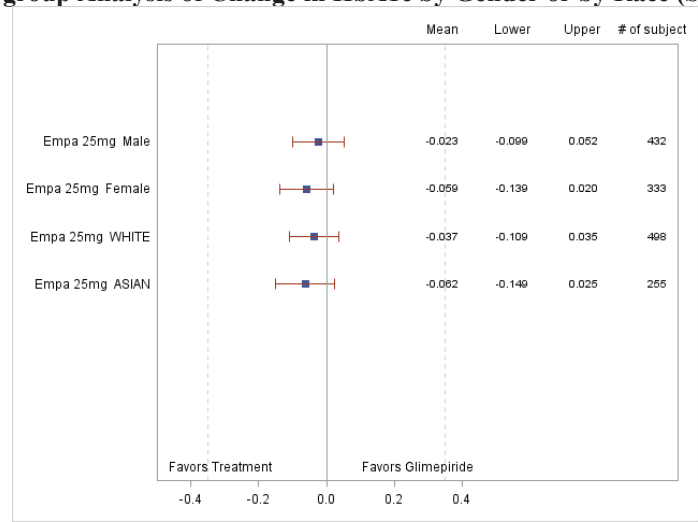
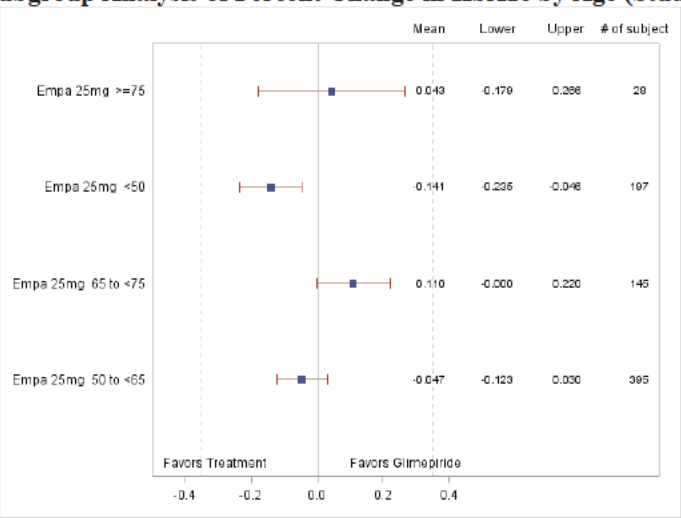


Figure 6 Subgroup Analysis of Percent Change in HbA1c by Age (Study 1245.28)



Empa+Met compared to Placebo (Study 1245.49)

(b) (4)

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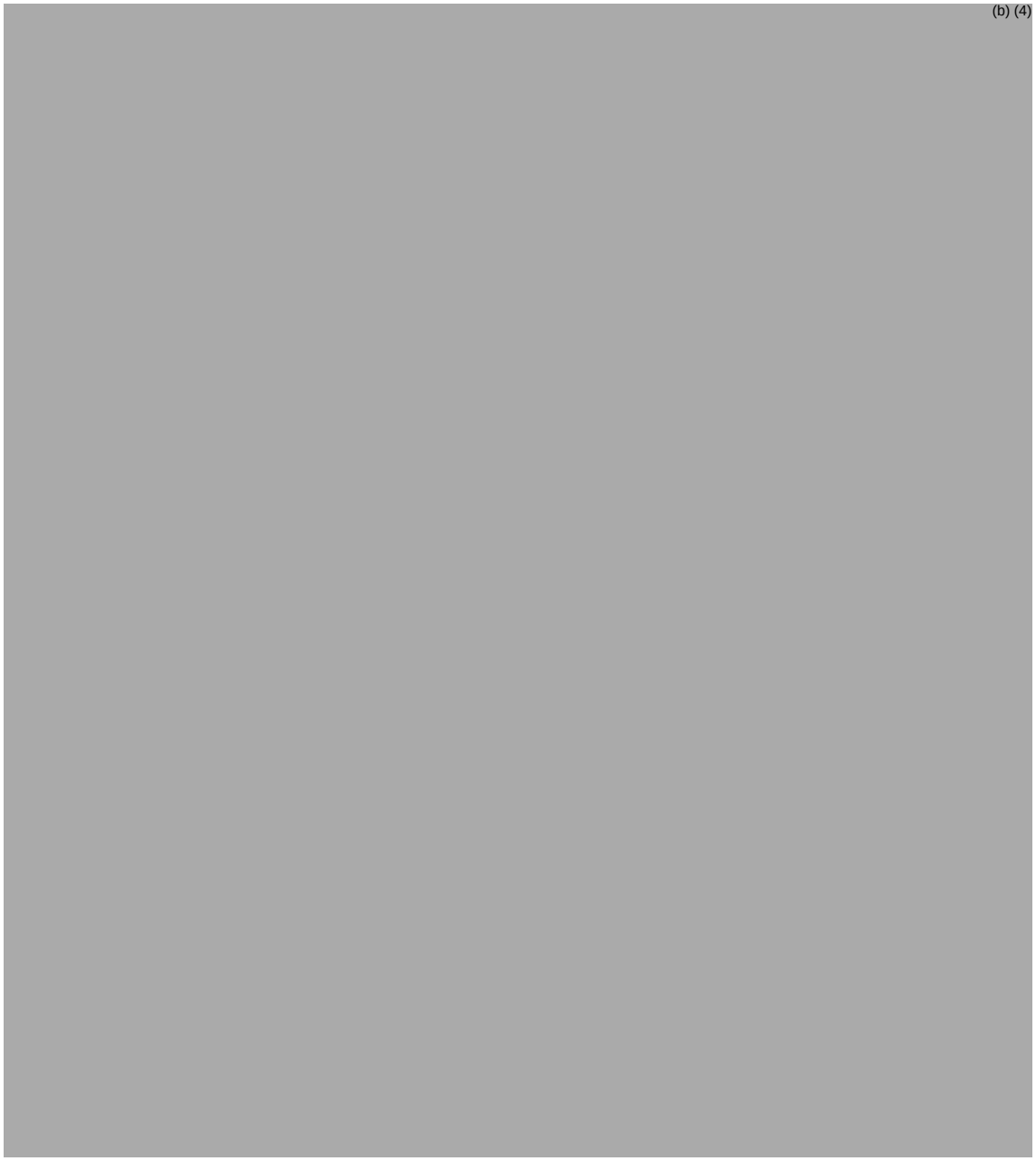


Twice Daily does / Once Daily does Compared to Placebo (Study 1276.10)

Comparison of the primary efficacy endpoint in subgroups investigated for twice daily does and single daily does were summarized in the following figures. No significant heterogeneity of treatment effect was found across subgroups in age, region, and gender. Race was not investigated in the subgroup analysis due to that over 85.5% patients were white.

Figure 11 Subgroup Analysis on Change in HbA1c (%) by Age (Study 1276.10)

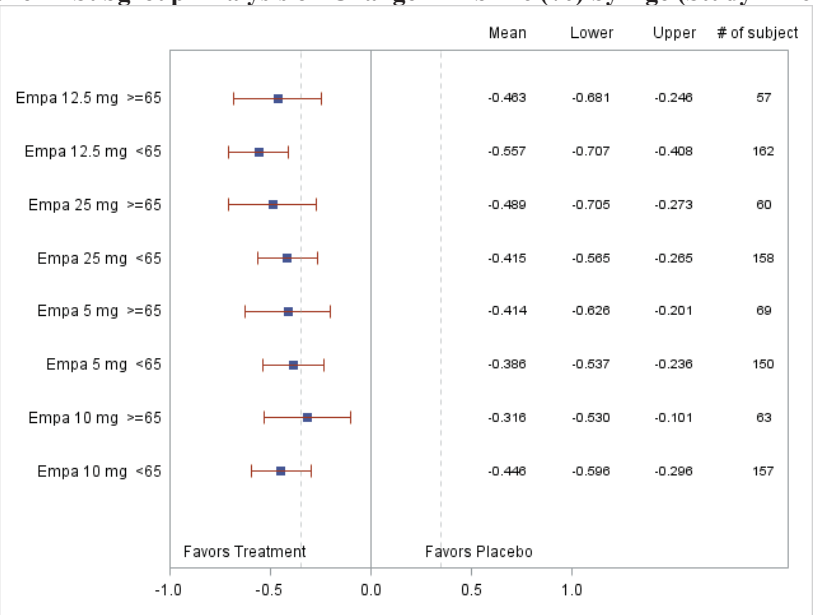


Figure 12 Subgroup Analysis on Change in HbA1c (%) by Region (Study 1276.10)

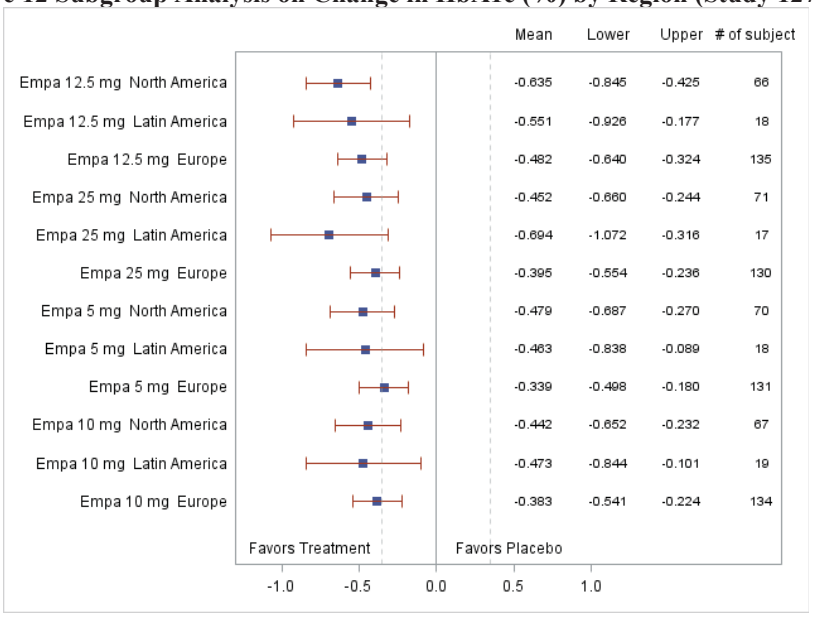


Figure 13 Subgroup Analysis on Change in HbA1c (%) by Gender (Study 1276.10)

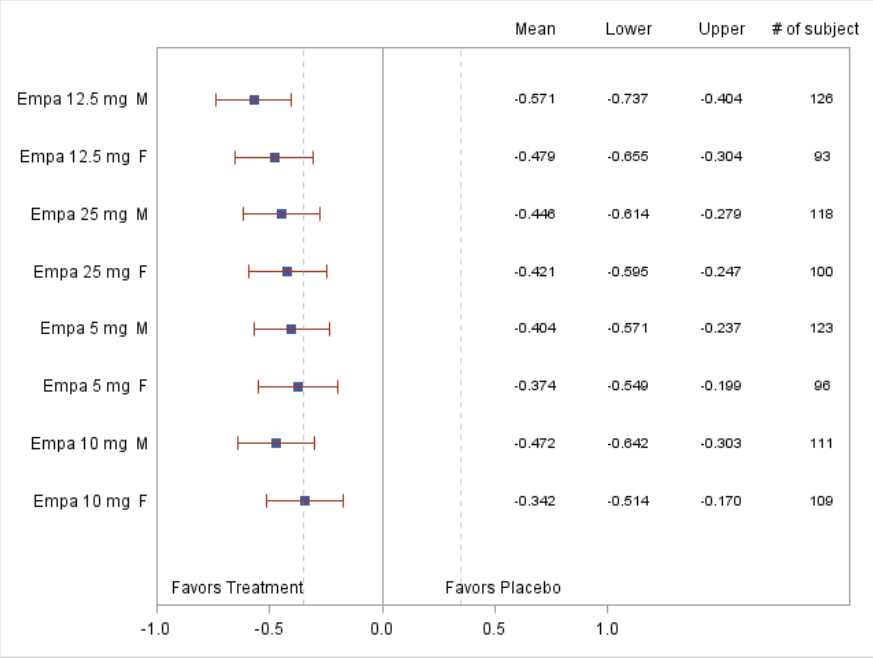


Figure 14 Subgroup Analysis on Change in HbA1c (%) by Baseline HbA1c (Study 1276.10)

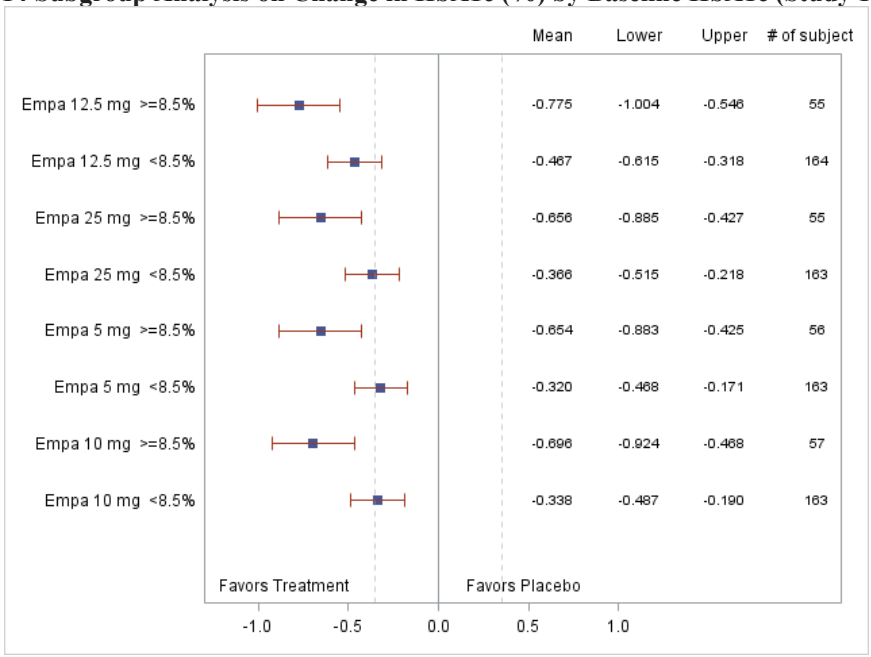
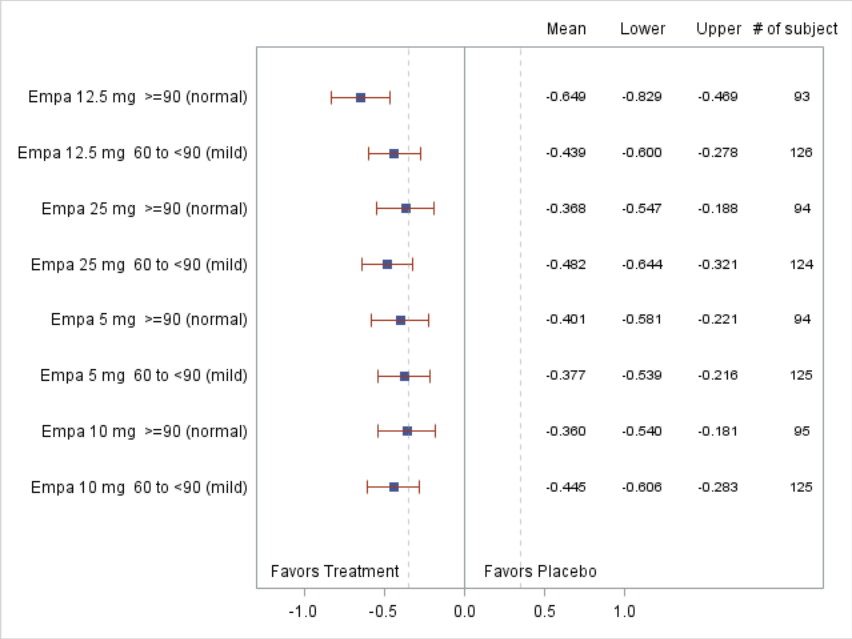


Figure 15 Subgroup Analysis on Change in HbA1c (%) by Baseline Renal Function (Study 1276.10)



5 SUMMARY AND CONCLUSIONS

5.1 Conclusion and Recommendations

The primary study endpoint was change in HbA1c from baseline to week 104 (study 1245.28) or week 18 week (study 1245.49) or week 16 (study 1276.10). Empagliflozin 25mg or 10mg were investigated. Both doses achieved statistically significant reduction of HbA1c compared to placebo. Empagliflozin 25mg was non-inferior to Glimepiride in changing HbA1c among type 2 diabetic patients when added to background therapy metformin. Twice administrated daily dose (Empa 5mg, 12.5mg) is non-inferior to once administrated daily dose (Empa 10mg, 25mg) on reduction of HbA1c. (b) (4)

The review on efficacy supports the clam of using empagliflozin for improving glycemic control in adult patients with T2DM with add-on metformin therapy. Based on results found in this review, this NDA is approvable from statistical point of view.

5.2 Labelling Recommendation

1. The most appropriate statistical analysis provided in the product label should not use LOCF (which is no longer supported by the Division). The sponsor did not provide an adequate reason why LOCF was appropriate. Additionally, the most appropriate statistical analysis for the product label should include measurements for HbA1c after discontinuing the initial protocol treatment as adherence tends to be an effect modifier and this is consistent with the design and conduct of the study.

2. I would recommend reporting non-inferiority [redacted] (b) (4)

3. I would not recommend Study 1245.49 to be included in the labeling for empagliflozin and metformin combination use, despite the ad-hoc subgroup analysis showed that no significant reduction in HbA1c was found between the two subgroups of insulin use only and insulin+metformin.

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/s/

SHUXIAN Z SINKS
04/15/2015

MARK D ROTHMANN
04/16/2015
I concur

STATISTICS FILING CHECKLIST FOR NDA 206111

NDA Number: 206111 **Applicant:** Boehringer Ingelheim Pharmaceuticals **Stamp Date:** August 04, 2014

Drug Name: Empagliflozin/ Metformin FDC **NDA Type:** 505 (b)(2) Standard

On **initial** overview of the NDA application for RTF: Study 1245-0049

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comment:

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.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR NDA 206111

Brief Summary of Pivotal Studies

All subjects enrolled in the pivotal studies were patients with type 2 diabetes and insufficient glycemic control. The randomization of the pivotal studies was stratified by HbA1c, eGFR at visit 1 and geographical region. Subjects were randomized equally to either placebo, empagliflozin 10mg, or empagliflozin 25mg.

Trial 1245.23 were composed of two independent studies $1245.23_{(met)}$ and $1245.23_{(su)}$, where patients received different background therapies (metformin-only or metformin with sulfonylurea). Each study was a 24 week, Phase III randomized, multi-center, multi-national, double-blind, placebo-controlled study to investigate safety and efficacy of empagliflozin (10mg, 25mg administered orally once daily) compared to placebo. Clinical visits were screening (visit 1), Run-in (visit 2), baseline (visit 3), visit 4-6, end of treatment (visit 7, at the full 24-week), follow-up (visit 8). For each of the pivotal studies, the primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment.

Trial 1245.49 was a phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group to study the safety and efficacy of empagliflozin compared to placebo during 52 weeks in patients on multiple daily injections (MDI) insulin along or with metformin. Subjects were randomized equally to either placebo, empagliflozin 10mg, or empagliflozin 25mg. The primary endpoint is the change from baseline in HBA1c after 18 weeks.

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/s/

SHUXIAN Z SINKS
09/25/2014

MARK D ROTHMANN
09/26/2014
Concur