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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

Boehringer Ingelheim has submitted a new drug application (NDA) for the triple fixed dose combination (FDC) of empagliflozin, linagliptin, and metformin HCl extended-release tablets for the improvement of glycemic control in adults with type 2 diabetes mellitus (T2DM) ^{(b) (4)}. The maximum recommended dose of the triple FDC is 25 mg empagliflozin, 5 mg linagliptin and 2000 mg metformin HCl. Each individual component has been approved and available in the US for the treatment of T2DM. Glyxambi[®], the FDC of empagliflozin and linagliptin, was approved in the US in January 2015 as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.

During the IND review stage, the applicant identified three key Phase 3 studies where either empagliflozin and/or linagliptin was administered as add-on therapy to metformin to support the efficacy of the triple FDC. The factorial design study 1275.1 was previously reviewed (NDA 206-073) for the approval of Glyxambi and proposed to be incorporated into the labeling for the triple FDC as a cross-reference¹. The add-on studies 1275.9 and 1275.10 were non-responder studies conducted to support the registration of empagliflozin and linagliptin FDC in Europe. The results from these two studies were not available at the time the application of Glyxambi was submitted to the FDA. FDA recommended submitting the clinical trial reports and datasets although these two studies were deemed supportive studies and not included in the labeling. Per this request, the applicant submitted clinical trial reports and datasets for studies 1275.9 and 1275.10 in this NDA submission. No new indication or any labeling change was proposed.

There is no major statistical issue identified in this submission. The analyses results for Studies 1275.9 and 1275.10 support that the triple FDC was superior in HbA1c, FPG, and body weight reduction (Study 1275.10) when compared to respective monotherapies (linagliptin 5 mg for Study 1275.9; empagliflozin 25 mg or 10 mg for Study 1275.10) on a metformin background therapy after 24 weeks of treatment.

¹ For detailed information regarding the efficacy evaluation for Study 1275.1, please refer to Dr. Jennifer Clark's statistical review dated October 15, 2014.

2 INTRODUCTION

2.1 Overview

Boehringer Ingelheim has submitted an NDA for the triple fixed dose combination (FDC) of empagliflozin, linagliptin, and metformin HCl extended-release tablets for the improvement of glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4)

. The maximum recommended dose of the triple FDC is 25 mg empagliflozin, 5 mg linagliptin and 2000 mg metformin HCl. Each individual component has been approved and available in the US for the treatment of T2DM. Glyxambi®, the FDC of empagliflozin (25 mg or 10 mg) and linagliptin (5 mg), was approved in the US in January 2015 as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.

During the IND review stage, the applicant identified three key studies where either empagliflozin and/or linagliptin was administered as add-on therapy to metformin to support the efficacy of the triple FDC. The factorial design study 1275.1 was conducted to support the approval of Glyxambi. The study compared empagliflozin and linagliptin FDC group to the individual components in treatment naïve and metformin treated patients with T2DM. Study 1275.1 was previously reviewed and proposed to be incorporated into the labeling for the triple FDC as a cross-reference. The add-on studies 1275.9 and 1275.10 were non-responder studies conducted to support the registration of empagliflozin and linagliptin FDC in Europe. The results from these two studies were not available at the time the application of Glyxambi was submitted. In the Pre-NDA meeting written response dated January 25, 2018, the applicant deemed Studies 1275.9 and 1275.10 as supportive studies for this NDA and proposed not to submit the clinical trial reports and datasets. However, FDA recommended submitting the clinical trial reports and datasets for additional information even though these two studies are not included in the labeling.

In response to an information request sent on May 6, 2019, the applicant presented and discussed the results from additional analyses on the primary and key secondary efficacy endpoints for Studies 1275.9 and 1275.10. Details will be discussed in Section 3.2. Since only supportive studies were submitted in this NDA submission, this review briefly discusses the evaluation of efficacy and only focuses on the analyses requested by FDA.

2.2 Data Sources

Documentation including the study protocol, statistical analysis plan (SAP), and clinical study report (CSR) were submitted in the original submission under the network path <\\CDSESUB1\evsprod\NDA212614\0000>. All the SDTM and ADaM datasets as well as the SAS programs were submitted under the same network path. Datasets were submitted by the applicant to the CDER electronic data room in SAS transport format.

On June 12, 2019, the applicant provided information request response and programs used in generating the results for additional analyses under the network path <\\CDSESUB1\evsprod\NDA212614\0007>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented. I was able to reproduce the results of primary and sensitivity analyses using the ADaM datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies 1275.9 and 1275.10 were similarly designed as multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled, add-on studies (Table 1). Eligible patients underwent a 16-week open-label period on metformin background therapy with adjunct linagliptin 5 mg (Study 1275.9) or adjunct empagliflozin (25 mg or 10 mg; Study 1275.10), followed by a 1-week open-label run-in period. Patients who completed the open-label run-in period and had met the inclusion criteria entered a 24-week double-blind treatment period and were randomized to add-on treatment of either empagliflozin (25 mg or 10 mg; Study 1275.9) or linagliptin 5 mg (Study 1275.10). Randomization was stratified by baseline HbA1c, baseline renal function, and region.

Table 1. Study Design

Study	Design	Treatment	Treated Set (N)
1275.9	24-week add-on study of Empa	Add-on to Met + Lina 5: <ul style="list-style-type: none">• Empa 25• Empa 10• Placebo	332
		Add-on to Met + Empa 25: <ul style="list-style-type: none">• Lina 5• Placebo	224
1275.10	24-week add-on study of Lina	Add-on to Met + Empa 10: <ul style="list-style-type: none">• Lina 5• Placebo	254

Empa: empagliflozin; Lina: linagliptin; Met: metformin
Source: Reviewer

Patients were instructed to take the study medication daily. Patients who needed rescue medication before baseline were to be discontinued from open-label treatment and were not eligible for randomization into the double-blind period of the trial. During the double-blind treatment period, patients visited the study site at Weeks 0 (baseline), 6, 12, 18, 24 for assessments of efficacy.

The primary and key secondary efficacy endpoints for Study 1275.9 were:

- 1) HbA1c (%) change from baseline to Week 24 after the first dose of treatment (primary);
- 2) Fasting plasma glucose (FPG) (mmol/L) change from baseline to Week 24 after the first dose of treatment (key secondary);
- 3) Body weight (kg) change from baseline to Week 24 after the first dose of treatment (key secondary).

The primary and key secondary efficacy endpoints for Study 1275.10 were:

- 1) HbA1c (%) change from baseline to Week 24 after the first dose of treatment (primary);
- 2) FPG change from baseline to Week 24 after the first dose of treatment (key secondary).

3.2.2 Statistical Methodologies

In Studies 1275.9 and 1275.10, the treated set (TS) consisted of patients who were randomized and treated with at least 1 dose of study medication during the double-blind period of the trial. Patient disposition and efficacy analyses were based on the TS.

According to the applicant, it was originally planned to use an analysis of covariance (ANCOVA) to analyze the primary endpoint but it was modified to use a mixed model with repeated measures (MMRM) in the protocol revision 2 (dated December 17, 2013) based on an advice letter from a health authority (See CSR Section 9.7.1.1). In both studies it was pre-specified to analyze the primary endpoint using an MMRM that included main effects of treatment, region, baseline renal function, visit, and visit-by-treatment interaction, and baseline HbA1c as a covariate. The key secondary endpoints were analyzed using the same model as pre-specified for the primary endpoint, with addition of the corresponding baseline variable (baseline FPG or baseline body weight) as a covariate. However, we have moved away from MMRM approach for primary analyses because of its missing at random (MAR) assumption. Instead, we prefer analyses that model the missing data based on available data from retrieved dropouts or consistent with what the data would have been (intent-to-treat estimand). All post-dropout data and rescue data should also be included in the analysis. Therefore, to implement our information request the applicant performed additional analyses for Studies 1275.9 and 1275.10 and submitted the results on June 12, 2019. In particular, an ANCOVA with multiple imputation washout method was used to analyze the primary and key secondary endpoints. Missing data in those endpoints from both treatment arms were imputed using observed data from the placebo arm. The imputation model was the same as pre-specified in the primary analysis. When impute missing data in the treatment arm, only baseline values and covariates were included in the model. When impute missing data in the placebo arm, baseline and intermediate values, as well as covariates from the placebo arm were included in the model. For sensitivity analysis a two-way tipping point analysis was used to evaluate the robustness of superiority in the primary endpoint. Estimated treatment difference was evaluated by varying imputed data in both treatment arms independently using the same ANCOVA model defined above.

A hierarchical testing procedure was applied to test the superiority of each add-on treatment arm, empagliflozin (25 mg or 10 mg; Study 1275.9) or linagliptin 5 mg (Study 1275.10), against placebo to control the overall alpha level at 0.05 in the order described above. Study 1275.10

was powered separately for each of the background empagliflozin doses, the statistical inference was also carried out separately for the subpopulations.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A summary of patient disposition is presented in Table 2. In Study 1275.9, 332 patients were randomly assigned to empagliflozin (110 patients in 25 mg; 112 patients in 10 mg) or placebo (110 patients) and treated. In Study 1275.10, 224 patients with background empagliflozin 25 mg (**Subpopulation A**) were randomly assigned to linagliptin 5 mg (112 patients) or placebo (112 patients) and treated; 254 patients with background empagliflozin 10 mg (**Subpopulation B**) were randomly assigned to linagliptin 5 mg (126 patients) or placebo (128 patients) and treated.

The rates of premature treatment discontinuation were less than 8% and 12% in Studies 1275.9 and 1275.10, respectively. The major reasons for early dropout were lost to follow-up and adverse event. Missing data in HbA1c at Week 24 were less than 6% and 10% in Studies 1275.9 and 1275.10, respectively.

Table 2. Patient Disposition

Study 1275.9	Metformin+lina 5 mg			
	Empa 25 mg N (%)	Empa 10 mg N (%)	Placebo N (%)	
Treated	110 (100.0)	112 (100.0)	110 (100.0)	
Not prematurely discontinued study medication	106 (96.4)	103 (92.0)	105 (95.5)	
Prematurely discontinued	4 (3.6)	9 (8.0)	5 (4.5)	
Adverse event	0	3 (2.7)	2 (1.8)	
Lack of efficacy	0	1 (0.9)	0	
Non-compliance to protocol	0	1 (0.9)	1 (0.9)	
Lost to follow-up	2 (1.8)	4 (3.6)	2 (1.8)	
Refused to continue study medication	2 (1.8)	0	0	
Study 1275.10	Metformin+empa 25 mg		Metformin+empa 10 mg	
	Lina 5 mg N (%)	Placebo N (%)	Lina 5 mg N (%)	Placebo N (%)
Treated	112 (100.0)	112 (100.0)	126 (100.0)	128 (100.0)
Not prematurely discontinued study medication	102 (91.1)	105 (93.8)	111 (88.1)	118 (92.2)
Prematurely discontinued	10 (8.9)	7 (6.3)	15 (11.9)	10 (7.8)
Adverse event	3 (2.7)	2 (1.8)	4 (3.2)	5 (3.9)
Lack of efficacy	0	1 (0.9)	0	0
Non-compliance to protocol	0	0	2 (1.6)	0
Lost to follow-up	5 (4.5)	2 (1.8)	4 (3.2)	1 (0.8)
Refused to continue study medication	0	1 (0.9)	1 (0.8)	2 (1.6)
Other	2 (1.8)	1 (0.9)	4 (3.2)	2 (1.6)

Empa: empagliflozin; Lina: linagliptin

Source: Reviewer

Demographic and baseline characteristics were generally balanced across the treatment arms (Tables 3 and 4). Overall, majority of patients were male (60% in Study 1275.9; 52% in Study 1275.10) and White (58% in Study 1275.9; 97% in Study 1275.10). The mean age in both studies was approximately 56 years.

Table 3. Demographic and Baseline Characteristics, Study 1275.9

	Metformin+lina 5 mg		
	Empa 25 mg	Empa 10 mg	Placebo
N	110	112	110
Age, mean (SD) [years]	55.4 (9.9)	54.3 (9.5)	55.9 (9.6)
Gender, N (%)			
Male	71 (64.5)	66 (58.9)	61 (55.5)
Female	39 (35.5)	46 (41.1)	49 (44.5)
Race, N (%)			
White	65 (59.1)	68 (60.7)	60 (54.6)
Asian	30 (27.3)	26 (23.2)	33 (30.0)
Black / African American	11 (10.0)	10 (8.9)	9 (8.2)
Other	4 (3.6)	8 (7.1)	8 (7.3)
Region, N (%)			
Europe	34 (30.9)	35 (31.3)	33 (30.0)
North America	38 (34.6)	40 (35.7)	37 (33.6)
Latin America	14 (12.7)	14 (12.5)	15 (13.6)
Asia	24 (21.8)	23 (20.5)	25 (22.7)
Time since diagnosis, N (%)			
≤1 year	7 (6.4)	6 (5.4)	9 (8.2)
>1 to 5 years	41 (37.3)	30 (27.5)	33 (30.0)
>5 to 10 years	35 (31.8)	44 (39.3)	38 (34.6)
>10 years	27 (24.5)	32 (28.6)	30 (27.3)
eGFR (MDRD), mean (SD)	93.4 (18.6)	90.4 (19.0)	93.0 (16.4)
HbA1c, mean (SD) [%]	8.0 (0.8)	8.0 (0.9)	8.0 (0.9)
FPG, mean (SD) [mmol/L]	9.4 (2.3)	9.3 (2.1)	9.1 (1.8)
Body weight, mean (SD) [kg]	84.4 (19.2)	88.3 (20.7)	82.3 (19.6)
BMI, mean (SD) [kg/m ²]	29.9 (5.3)	31.3 (5.9)	29.6 (5.7)

SD: standard deviation

MDRD: modification of diet in renal disease

Source: Reviewer

Table 4. Demographic and Baseline Characteristics, Study 1275.10

	Metformin+empa 25 mg		Metformin+empa 10 mg	
	Lina 5 mg	Placebo	Lina 5 mg	Placebo
N	112	112	126	128
Age, mean (SD) [years]	56.4 (9.9)	56.2 (10.7)	56.6 (9.5)	56.6 (9.5)
Gender, N (%)				
Male	54 (48.2)	65 (58.0)	71 (56.4)	72 (56.3)
Female	58 (51.8)	47 (42.0)	55 (43.6)	56 (43.7)
Race, N (%)				
White	109 (97.3)	108 (96.4)	123 (97.6)	122 (95.3)
Black / African American	3 (2.7)	4 (3.6)	2 (2.4)	3 (2.3)
Asian	0	0	0	1 (0.8)
Other	0	0	0	2 (1.6)
Region, N (%)				
Europe	51 (45.5)	52 (46.4)	63 (50.0)	63 (49.2)
North America	27 (24.1)	27 (24.1)	23 (18.2)	27 (21.1)
Latin America	34 (30.4)	33 (29.5)	40 (31.8)	38 (29.7)
Time since diagnosis, N (%)				
≤1 year	8 (7.1)	9 (8.0)	8 (6.4)	16 (12.5)
>1 to 5 years	31 (27.7)	34 (30.4)	44 (34.9)	42 (32.8)
>5 to 10 years	42 (37.5)	40 (35.7)	41 (32.5)	38 (29.7)
>10 years	31 (27.7)	29 (25.9)	33 (26.2)	32 (25.0)
eGFR (MDRD), mean (SD)	88.9 (18.7)	91.1 (19.7)	91.5 (19.5)	89.4 (19.6)
HbA1c, mean (SD) [%]	7.8 (0.7)	7.9 (0.9)	8.0 (1.0)	8.0 (0.9)
FPG, mean (SD) [mmol/L]	8.5 (1.7)	8.7 (2.1)	8.9 (2.3)	8.7 (1.9)
Body weight, mean (SD) [kg]	85.6 (16.7)	89.7 (16.1)	88.7 (16.9)	85.8 (18.1)
BMI, mean (SD) [kg/m ²]	30.7 (4.7)	31.9 (5.2)	31.4 (5.3)	30.9 (4.9)

SD: standard deviation

MDRD: modification of diet in renal disease

Source: Reviewer

3.2.4 Results and Conclusions

The results from the requested washout analyses of primary and key secondary endpoints for Studies 1275.9 and 1275.10 are presented in Tables 5 and 6, respectively. The results were similar to the applicant's MMRM analysis results. For Study 1275.9, on metformin background therapy with adjunct linagliptin 5 mg, the add-on treatment empagliflozin (25 mg or 10 mg) was statistically significantly superior (p-values <0.001) to placebo with respect to change from baseline to Week 24 in HbA1c, FPG, and body weight. Patients who received both empagliflozin doses as add-on treatment had significantly lower HbA1c, FPG, and body weight compared with patients who received placebo as add-on treatment.

Table 5. Analyses of Primary and Key Secondary Endpoints, Study 1275.9

Study 1275.9 ¹	Metformin+lina 5 mg		
	Empa 25 mg	Empa 10 mg	Placebo
Total patients analyzed, N	110	112	110
Mean baseline HbA _{1c} (SE)	7.97 (0.08)	8.00 (0.08)	7.99 (0.08)
Change from baseline			
Mean HbA _{1c} (SE)	-0.55 (0.09)	-0.61 (0.10)	0.06 (0.09)
Adjusted ² mean HbA _{1c} (SE)	-0.56 (0.08)	-0.61 (0.08)	0.07 (0.08)
Comparison vs. placebo			
Adjusted ² mean HbA _{1c} (SE)	-0.63 (0.11)	-0.69 (0.12)	
95% CI	(-0.86, -0.41)	(-0.91, -0.46)	
p-value	<0.0001	<0.0001	
Mean baseline FPG (SE)	169.9 (4.0)	168.0 (3.7)	163.2 (3.1)
Change from baseline			
Mean FPG (SE)	-31.7 (4.5)	-24.0 (4.1)	6.4 (4.6)
Adjusted ² mean FPG (SE)	-29.9 (3.7)	-23.4 (3.6)	4.0 (3.6)
Comparison vs. placebo			
Adjusted ² mean FPG (SE)	-33.9 (5.2)	-27.3 (5.1)	
95% CI	(-44.0, -23.7)	(-37.4, -17.3)	
p-value	<0.0001	<0.0001	
Mean baseline body weight (SE)	84.38 (1.83)	88.33 (1.95)	82.26 (1.87)
Change from baseline			
Mean body weight (SE)	-2.38 (0.25)	-2.78 (0.26)	-0.15 (0.25)
Adjusted ² mean body weight (SE)	-2.40 (0.25)	-2.71 (0.25)	-0.21 (0.25)
Comparison vs. placebo			
Adjusted ² mean body weight (SE)	-2.19 (0.35)	-2.50 (0.35)	
95% CI	(-2.87, -1.51)	(-3.20, -1.81)	
p-value	<0.0001	<0.0001	

SE: standard error

Empa: empagliflozin; Lina: linagliptin

¹ The results were based on the requested washout analyses where missing data in an endpoint from both arms were imputed using observed data from the placebo arm.

² ANCOVA model included baseline HbA_{1c} as linear covariate and baseline eGFR, geographical region, and treatment as fixed effects.

Source: IR response, modified Table 3

In Study 1275.10, on metformin background therapy with adjunct empagliflozin (25 mg or 10 mg), the add-on treatment linagliptin 5 mg was statistically significantly superior (p-values <0.001) to placebo with respect to change from baseline to Week 24 in HbA_{1c}. For both subpopulations, patients who received linagliptin 5 mg as add-on treatment had significantly lower HbA_{1c} compared with patients who received placebo as add-on treatment. While patients who received linagliptin 5 mg had numerically lower FPG compared with patients who received placebo in both subpopulations, treatment difference between two arms became non-significant (p=0.139) in Subpopulation A. In the applicant's pre-specified primary analysis, the results for Subpopulation A were borderline significant (-7.9 [-15.6, -0.2]; p=0.045).

Table 6. Analyses of Primary and Key Secondary Endpoints, Study 1275.10

Study 1275.10 ¹	Metformin+empa 25 mg		Metformin+empa 10 mg	
	Lina 5 mg	Placebo	Lina 5 mg	Placebo
Total patients analyzed, N	112	112	126	128
Mean baseline HbA _{1c} (SE)	7.83 (0.07)	7.89 (0.08)	8.03 (0.08)	8.01 (0.08)
Change from baseline				
Mean HbA _{1c} (SE)	-0.55 (0.07)	-0.17 (0.07)	-0.56 (0.09)	-0.23 (0.07)
Adjusted ² mean HbA _{1c} (SE)	-0.56 (0.07)	-0.15 (0.07)	-0.56 (0.07)	-0.23 (0.07)
Comparison vs. placebo				
Adjusted ² mean HbA _{1c} (SE)	-0.40 (0.10)		-0.34 (0.10)	
95% CI	(-0.59, -0.22)		(-0.53, -0.15)	
p-value	<0.0001		0.0006	
Mean baseline FPG (SE)	152.9 (2.8)	156.1 (3.5)	160.6 (3.6)	156.6 (3.1)
Change from baseline				
Mean FPG (SE)	-10.2 (3.4)	-6.0 (3.3)	-9.8 (4.5)	3.1 (3.0)
Adjusted ² mean FPG (SE)	-11.0 (2.8)	-5.2 (2.7)	-8.3 (3.2)	1.7 (3.1)
Comparison vs. placebo				
Adjusted ² mean FPG (SE)	-5.8 (3.9)		-10.0 (4.5)	
95% CI	(-13.4, 1.9)		(-18.7, -1.2)	
p-value	0.1391		0.0254	

SE: standard error

Empa: empagliflozin; Lina: linagliptin

¹ The results were based on the requested washout analyses where missing data in an endpoint from both arms were imputed using observed data from the placebo arm.

² ANCOVA model included baseline HbA_{1c} as linear covariate and baseline eGFR, geographical region, and treatment as fixed effects.

Source: IR response, modified Table 5

For tipping point analysis (results not included in this review), the applicant explored scenarios for HbA_{1c} adjustment values ranging from -0.4 to 2.0 for each active arm and from -1.6 to 2.0 for each placebo arm. In Study 1275.9, the results remained consistent with those of the requested analysis for all scenarios. In Study 1275.10, add-on treatment differences in primary endpoint between two arms remain statistically significant for all scenarios in Subpopulation B. In Subpopulation A, however, add-on treatment differences became non-significant when the adjustment value is large for active arm and/or the value is small for placebo arm. Given the fact that the affected scenarios are clinically implausible and very unlikely, the results of the requested analysis are considered robust.

3.3 Evaluation of Safety

The safety of the triple FDC was evaluated in the Phase 3 Studies 1275.9, 1275.10, and 1275.1, and the Phase 1 bioequivalence studies 1361.3, and 1361.11. Study 1275.1 has been reviewed for the approval of Glyxambi. There were no safety issues in the two Phase 1 studies.

The number and proportion of patients with hypoglycemia were low and comparable across treatment arms in both studies. In Study 1275.9, more patients were reported with at least 1 AE in the placebo arm (68%) compared to the empagliflozin arm (52% in 25 mg; 55% in 10 mg). Similarly, in Study 1275.10, more patients were reported with at least 1 AE in the placebo arm (59% in Subpopulation A; 56% in Subpopulation B) compared to the linagliptin arm (53% in

Subpopulation A; 48% in Subpopulation B). The most frequently observed AEs in all controlled studies were infections of the urinary tract and infections of the upper respiratory tract. No deaths were reported during the double-blind treatment period in Studies 1275.9 or 1275.10. For both studies, there were less patients with serious adverse events (SAEs) in the active arm than in the corresponding placebo arm. In Study 1275.9, there were 9 patients in the empagliflozin arm (4 patients [4%] in 25 mg; 5 patients [5%] in 10 mg) and 10 patients (9%) in the placebo arm reported with SAEs. In Study 1275.10, there were 7 patients in the linagliptin arm (3 patients [3%] in Subpopulation A; 4 patients [3%] in Subpopulation B) and 9 patients in the placebo arm (4 patients [4%] in Subpopulation A; 5 patients [4%] in Subpopulation B) reported with SAEs. Please refer to Dr. Frank Pucino's review for detailed information regarding the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were performed by the following categories:

- Gender (male and female)
- Race (Caucasian, Black, Asian, and Other)
- Age (<65 years, 65 to <75 years, and 75 to <85 years)
- Region (North America, Europe, Asia, and Latin America)
- Ethnicity (Hispanic/Latino and not Hispanic/Latino)
- Baseline HbA1c (<8.5%, \geq 8.5%)
- Baseline renal function (normal eGFR \geq 90 mL/min/1.73m²; mild impairment eGFR 60 to <90 mL/min/1.73m²)
- Metformin posology (850 bid, 1000 bid, and other)
- Baseline BMI (<25, 25 to <30, 30 to <35, and \geq 35)
- Baseline weight (\leq 70 kg, >70 to \leq 80 kg, >80 to \leq 90 kg, and >90 kg)
- Time since diagnosis of T2DM (\leq 1 year, >1 to 5 years, >5 to 10 years, and >10 years)

The results were generally consistent across subgroup categories and confirmed the results of the primary analysis. There were generally no indications of treatment by subgroup interactions (p-values \geq 0.1). Potential impact of baseline HbA1c and the time since diagnosis on the treatment effect were detected in Study 1275.9. Patients with a higher baseline HbA1c had a larger treatment effect in the empagliflozin 25 mg group (-0.51% [-0.78, -0.24] for baseline HbA1c<8.5%; -1.25% [-1.70, -0.79] for baseline HbA1c \geq 8.5%) and in the empa 10 mg group (-0.62% [-0.89, -0.35] for baseline HbA1c<8.5%; -1.25% [-1.70, -0.80] for baseline HbA1c \geq 8.5%). Patients with a shorter time since diagnosis had a larger treatment effect. This trend was more prominent in the empagliflozin 25 mg group (-1.45% [-2.30, -0.60] for time since diagnosis \leq 1 year; -0.22% [-0.68, 0.23] >10 years).

5 SUMMARY AND CONCLUSIONS

5.1 Discussion and Conclusions

In Study 1275.9, statistically significant improvements in HbA1c, FPG, and body weight were observed for add-on treatment of empagliflozin (25 mg or 10 mg) on metformin background therapy with adjunct linagliptin 5 mg compared with placebo as add-on treatment after 24 weeks of treatment in patients with T2DM.

In Study 1275.10, statistically significant improvements in HbA1c were observed for add-on treatment of linagliptin 5 mg on metformin background therapy with adjunct empagliflozin (25 mg or 10 mg) compared with placebo as add-on treatment after 24 weeks of treatment in patients with T2DM. While statistically significant improvement in FPG was observed for add-on treatment of linagliptin 5 mg on metformin background therapy with adjunct empagliflozin 10 mg compared with placebo, clinically meaningful but statistically non-significant improvement was observed for add-on treatment of linagliptin 5 mg on metformin with adjunct empagliflozin 25 mg.

Glyxambi was approved in the US in January 2015 based on factorial design Study 1275.1. These two Phase 3 studies (1275.9 and 1275.10) were submitted to support the efficacy and safety of the triple FDC per FDA's request. There is no major statistical issue identified in this submission. The analyses results for Studies 1275.9 and 1275.10 support that the triple FDC was superior in HbA1c, FPG, and body weight reduction when compared to respective monotherapies (linagliptin 5 mg for Study 1275.9; empagliflozin 25 mg or 10 mg for Study 1275.10) on a metformin background therapy after 24 weeks of treatment.

5.2 Labeling Recommendations

No labeling recommendations because Studies 1275.9 and 1275.10 were supportive studies and results will not be included in the product labeling.

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