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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Applicant: Boehringer Ingelheim
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1 EXECUTIVE SUMMARY

This is a statistical review for Boehringer Ingelheim's submission of empagliflozin/linagliptin combination as treatment for type 2 diabetes mellitus (T2DM). The applicant is seeking approval based on a change from baseline in glycosylated hemoglobin (HbA1c) at week 24. A low fixed dose combination (FDC) of empagliflozin 10 mg + linagliptin 5 mg as well as a high FDC of empagliflozin 25 mg + linagliptin 5 mg were studied against their monotherapy counterparts. Analysis results from this study are presented in this review

1.1 Conclusions and Recommendations

The submitted study for FDC empagliflozin/linagliptin showed some efficacy benefits when compared with monotherapy. While the trial did not show significant improvements in the treatment naïve population, it did show statistically significant improvements in the metformin treated subjects.

The lack of evidence showing an improvement in efficacy when comparing high FDC to low FDC does leave some reservations on the need for the higher dose. The findings in this review support approvability of FDC in the metformin population.

1.2 Brief Overview of Clinical Studies

There was one clinical study, BI Trial No. 1275.1, for empagliflozin (BI 10773) / linagliptin (BI 1356) combination. This was a phase III randomized, multi-national, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of low and high fixed dose combination (FDC) tablets compared with the individual components (BI 10773 25 mg, BI 107723 10 mg, and linagliptin 5 mg) for 52 weeks, with the primary endpoint taken at week 24. The study was stratified and analyzed separately for two different populations, treatment naïve and metformin treated patients with type 2 diabetes mellitus and having insufficient glycemic control. The results given in this review are based on separate analyses for each population. The trial lasted from 21 August 2011 to 10 September 2013. A hierarchical testing procedure was specified for each population. Due to the ordering of this procedure, all of the primary and secondary endpoints in the treatment naïve population were considered to be exploratory. The results found for this review, using methods similar to what was specified in the protocol, are given in Figure 1 and Figure 2. Results for endpoints shown in grey boxes should only be considered exploratory, even when $p < 0.05$, due to the protocol specified testing hierarchy.

The protocol specified a comparison of each FDC with respective monotherapies to show improved efficacy. There was, however, no specification for testing whether the higher FDC had any greater efficacy than the low FDC. Analyses done in this review showed a non-significant difference of -0.11 (-0.28, 0.06) in the metformin treated population and 0.15 (-0.05, 0.35) in the treatment naïve population. Sample size calculations done by the applicant during the IND stage

(IND 108388) were run based on an effect size of 0.5% between FDC and all monotherapies for change in HbA1c. Using this effect size for a post-hoc power calculation comparing low and high FDC, we see that this study appears to be adequately powered to detect such a difference between FDC in both populations. Since a significant effect of 0.5% remains outside both confidence intervals, we maintain reservations on whether the use of high FDC provides any meaningful difference when compared with low FDC.

Subgroup analyses of this combination confirmed previous findings in the empagliflozin monotherapy trials of possible interactions of treatment with renal function (See the statistical review for NDA 204629 by Dr. Dongmei Liu, signed October 30, 2013). Since such interactions did not preclude the approval of empagliflozin as monotherapy for T2DM, it will not be further discussed here.

Analysis results following the pre-specified hypothesis testing hierarchy for primary and key secondary endpoints, which are in line with what is in the study report, are shown in Figure 1 and Figure 2. Although the trial failed for the treatment naïve population when using the hierarchy, there does appear to be improvements in efficacy when compared with some monotherapies, but because of specifications within the protocol, these can only be considered “exploratory”.

There is the possibility that the trial failed not because the FDC treatment was not any better than monotherapy in the treatment naïve population, but because there may be an efficacy “ceiling”. Treatment naïve subjects given empagliflozin 25 mg monotherapy seem to hit this ceiling, so adding linagliptin to this treatment would not result in added benefit. Results seen with empagliflozin 10 mg indicate there may still be room for additional benefit. Proving the existence of such a ceiling effect would be difficult and beyond the scope of this study.

Figure 1: Testing Hierarchy Results for Metformin Treated Subjects

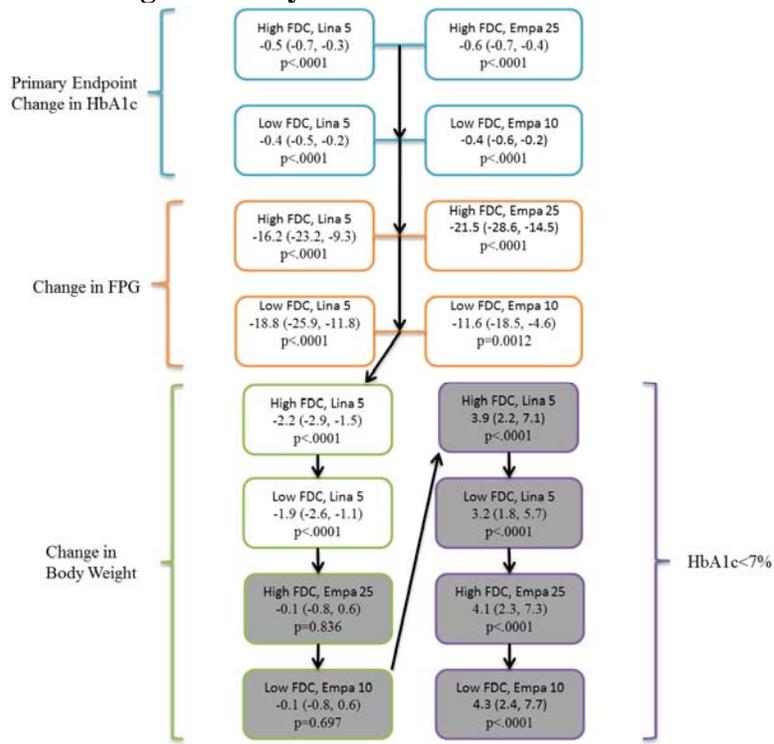
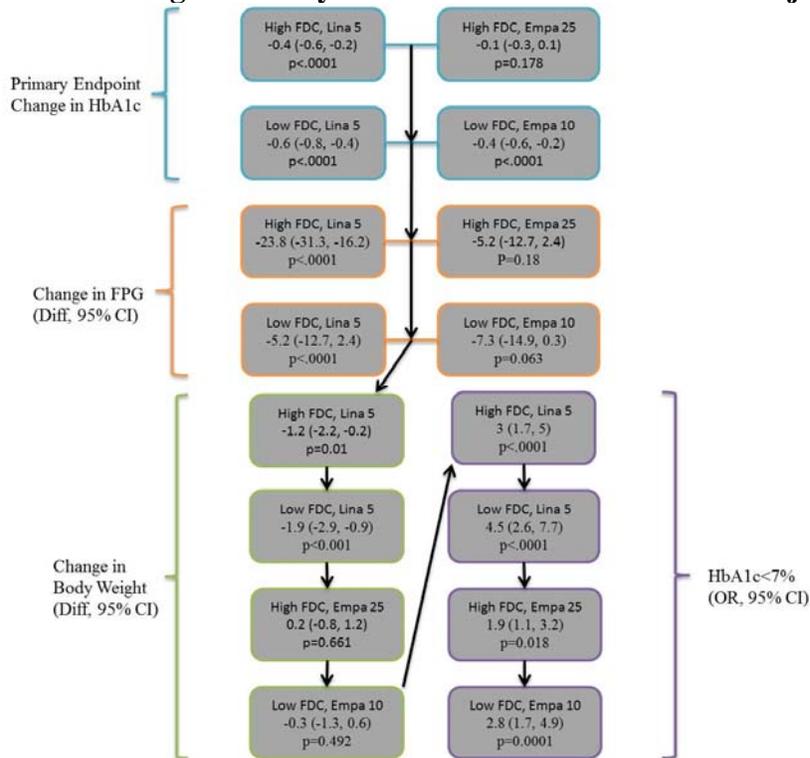


Figure 2: Testing Hierarchy Results for Treatment Naive Subjects



1.3 Statistical Issues and Concerns

There were several concerns that emerged during the course of this review. One had to do with failure of part of the trial due to the specification of the hierarchical testing procedure. The other concern had to do with an absence of methods to show increased efficacy of high FDC over low FDC.

- The biggest statistical issue for this study has to do with the failure of the primary and all secondary endpoints in achieving statistical significance as was pre-specified for the treatment naïve population. While there did appear to be some evidence of improved efficacy in this population, these results must be considered “exploratory”, as deemed by the protocol, (b) (4).
- A separate issue with this submission has to do with the lack of evidence of improved efficacy in both populations when comparing high FDC to low FDC. This was neither specified in the protocol nor provided in the submission. Post-hoc analyses to test if the two FDCs were equivalent failed to show evidence of improved efficacy in terms of the chosen endpoints for the high FDC.
- Trial results for each population were not supportive of each other as analysis results were not significant for one population.

2 INTRODUCTION

2.1 Overview

BI 10773/linagliptin is a combination product of two oral antidiabetic agents for the treatment of type 2 diabetes mellitus (T2DM). Linagliptin as a monoproduct was approved on May 2, 2011 under NDA 201280 and is currently available under the name Tradjenta. Empagliflozin was submitted for approval as a monotherapy on March 5, 2013 under NDA 204629 and was subsequently approved under will be marketed under the trade name Jardiance. The proposed name and indication for this fixed-dose combination (FDC) tablet is Glyxambi which is to be “an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate.” The current study examined safety and efficacy in both treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycemic control. This was a 52 week phase 3 randomized, double-blind, parallel group study with five treatment arms, Empagliflozin 25mg/Linagliptin 5 mg ($n_{\text{metformin}}=137$, $n_{\text{naïve}}=137$), Empagliflozin 10mg/Linagliptin 5 mg ($n_{\text{metformin}}=135$, $n_{\text{naïve}}=136$), Empagliflozin 25mg ($n_{\text{metformin}}=141$, $n_{\text{naïve}}=135$), Empagliflozin 10mg ($n_{\text{metformin}}=140$, $n_{\text{naïve}}=134$), and Linagliptin 5 mg ($n_{\text{metformin}}=132$, $n_{\text{naïve}}=135$).

2.1.1 History of Drug Development

Empagliflozin is an oral selective inhibitor of SGLT-2 which was reviewed and approved for treatment levels of 10 mg and 25 mg daily. Previous phase 3 studies compared empagliflozin as a monotherapy or add on to metformin or other therapies to placebo. Table 1, copied from the proposed label, shows study results for empagliflozin (Jardiance) as monotherapy compared with placebo. This study demonstrated an improvement in lowering HbA1c below 7%, fasting plasma glucose, and body weight with both low and high dose empagliflozin when compared to placebo.

Table 1: Efficacy Results in Proposed Label for Empagliflozin Monotherapy compared to Placebo



(b) (4)

Linagliptin is a DPP-4 activity inhibitor, prolonging the half-life of GLP-1, which can be administered orally or intravenously. Clinical studies run by the applicant indicated that for this treatment there were no relevant interactions with metformin, pioglitazone, glyburide, or empagliflozin. Previous phase 3 studies compared 5 mg linagliptin (trade name Tradjenta) with placebo, metformin, and various combinations of linagliptin and metformin. Results from the product label for Tradjenta are given in Table 2. The applicant was able to show a statistically significant difference in the change from baseline in A1C (%) and FPG when compared with placebo. There does not seem to be a difference in the proportion of patients achieving A1C under 7% in this study, though.

Table 2: Efficacy Results from the label for Linagliptin (Tradjenta) compared to Placebo

	Placebo	TRADJENTA 5 mg Once Daily*	Metformin 500 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily	Metformin 1000 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 1000 mg Twice Daily
A1C (%)						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean****)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients [n (%)] achieving A1C <7%***	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG (mg/dL)						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	203	195	191	199	191	196
Change from baseline (adjusted mean****)	10	-9	-16	-33	-32	-49
Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

*Total daily dose of TRADJENTA is equal to 5 mg

**Full analysis population using last observation on study

***Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 mg twice daily, n=136; Metformin 1000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1000 mg twice daily, n=138

****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Since empagliflozin inhibits SGLT-2 and linagliptin inhibits DPP-4, the applicant rationalizes that the combination of the two “may lead to additional effects on glycemic control.” The convenience factor of having only one tablet instead of two is also offered as further justification for this combination.

2.2 Data Sources

The data and final study report were submitted electronically and archived under the network path location <\\CDSesub1\evsprod\NDA206073\206073.enx>. The information needed for this review was contained in Module 1 FDA Regional information (cover letter, meetings, response to information requests) and Module 5 (clinical study reports). Independent coding for the analysis was run for this review. An information request was made for the applicant’s analysis code for verification.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This submission is in the electronic common technical document (eCTD) form with an xml backbone. A statistical analysis plan was pre-specified in section 7 of the protocol and further detailed in a separate SAP. The methods described in this plan along with other sensitivity analyses were used in this review. Study datasets were provided as SAS XPORT transport files.

The clinical study report mentions a monitoring visit on February 21, 2012 which turned up evidence of scientific and data misconduct in a site in the USA recording fraudulent data. This

site was closed and subjects were sent to a new site which was opened to replace the old one. It was also found that several patients were screened/randomized at multiple sites within the study which increased the patient numbers by 23. The multiple screenings/randomization of patients were in 13 sites, two of which only contained subjects with these violations. Data from the patients at the fraudulent site and those with multiple screenings/randomization were excluded from the primary analysis and clinical study report.

Original datasets were submitted and used for the initial analysis for this review. Analysis datasets were inadvertently omitted from the original submission and later sent on May 7, 2014 under the sequence number 0005.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Objectives

This was a phase III randomized, multi-national, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5mg Fixed Dose Combination Tablets compared with the individual components (BI 10773 25 mg, BI 107723 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycemic control. The study was powered to analyze two separate patient groups at week 24, metformin treated and treatment naïve patients. Statistical inference was carried out separately for each population.

The study consisted of five periods, screening, placebo run-in, treatment phase in one of five treatment arms (Empagliflozin 25mg/Linagliptin 5mg, Empagliflozin 10mg/Linagliptin 5mg, Empagliflozin 25mg, Empagliflozin 10mg, and Linagliptin 5mg), post-treatment, and post-study. After a 2 week run-in period patients were randomized, stratified by patient population, to one of five treatment arms for the 52 week treatment period.

Table 3: Applicant created table of Treatment Regimens/Study Intervals for 24 Week Analysis

Label	Interval	Start/stop ^a date	Start/stop ^b time
Screening	Screening	Start date: Date of informed consent	00:00
Run-in	Run-in	Start date: Date of first administration of run-in medication	Time of first administration of run-in medication 12:00 if missing
Empagliflozin 10mg Empagliflozin 25mg Linagliptin 5mg Empagliflozin 25mg/ Linagliptin 5mg FDC Empagliflozin 10mg/ Linagliptin 5mg FDC	Treatment	Start date: date of first administration of study medication Stop date: min(Date of last intake of study drug + X day, cutoff date, 182 days after (including) first intake)	Start time: time of first administration of study medication, 12:00 if missing Stop time: time of last administration of study medication, 23:59
Post-treatment	Post-treatment	Start date: If treatment stop date + X < min(cutoff date, 182 days after (including) first intake), then start date = treatment stop date + X + 1 Otherwise, no post-treatment period.	00:00
Post-study	Post-study	Last contact date is defined as the maximum of (Trial Completion Date , Last Study Drug Intake + X) +1 If last contact day >= 182 days or not recorded, no post-study period. If last contact day < 182, then post-study starts at last contact day, and stops at min(cutoff, 182 days).	00:00

^a If stop date is unspecified, then the stop date is the start date of the next period -1.

^b if stop time is unspecified, then the stop time is the start time of the next period - 1 second.

X is 1, 3, or 7 days for pulse rate, safety laboratory, and AE respectively.

There were a total of 2504 patients enrolled with 1363 entering the study. The population was stratified by either having a metformin background (n=686) or treatment naïve patients (n=677). These were recruited in 188 centers with screenings across 22 countries in Asia (10.8%), Europe (27.7%), Latin America (11.5%), and North America (50% of the screened population).

For the metformin group, this was a multi-national study that included 1179 enrolled patients from 188 centers in 22 countries across Asia, Europe, Latin America, and North America. 686 patients were randomized to each arm in a 1:1:1:1 ratio. Some subjects were excluded from the applicant's analysis due to protocol violations described in section 3.1.

PATIENT POPULATION WITH METFORMIN BACKGROUND:

Entered: 686 patients
FDC empagliflozin 25 mg/linagliptin 5 mg:
entered: 137 treated: 137 analysed (for primary endpoint): 134
FDC empagliflozin 10 mg/linagliptin 5 mg:
entered: 136 treated: 136 analysed (for primary endpoint): 135
Empagliflozin 25 mg:
entered: 141 treated: 141 analysed (for primary endpoint): 140
Empagliflozin 10 mg:
entered: 140 treated: 140 analysed (for primary endpoint): 137
Linagliptin 5 mg:
entered: 132 treated: 132 analysed (for primary endpoint): 128

In the treatment naïve study population there were 1325 enrolled patients in the multi-national study from 201 centers across 22 countries in Asia, Europe, Latin America, and North America. There were 677 patients randomized in a 1:1:1:1:1 ratio.

TREATMENT NAÏVE PATIENT POPULATION:

Entered: 677 patients
FDC empagliflozin 25 mg/linagliptin 5 mg:
entered: 137 treated: 137 analysed (for primary endpoint): 134
FDC empagliflozin 10 mg/linagliptin 5 mg:
entered: 136 treated: 136 analysed (for primary endpoint): 135
Empagliflozin 25 mg:
entered: 135 treated: 135 analysed (for primary endpoint): 133
Empagliflozin 10 mg:
entered: 134 treated: 134 analysed (for primary endpoint): 132
Linagliptin 5 mg:
entered: 135 treated: 135 analysed (for primary endpoint): 133

Primary Efficacy Objective and Endpoint

The main objective of this study was to show superiority of the combination therapy of empagliflozin and linagliptin against the individual monotherapy components. With this study objective in mind, the applicant used a primary efficacy endpoint of change from baseline in HbA1c (%) at 24 weeks of treatment.

Key Secondary Endpoints

The key secondary endpoints listed in the protocol were to be tested hierarchically in the following order:

1. Change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment
2. Change from baseline in body weight after 24 weeks of treatment

In an amendment to the original protocol an exploratory endpoint was taken to be the third key secondary endpoint,

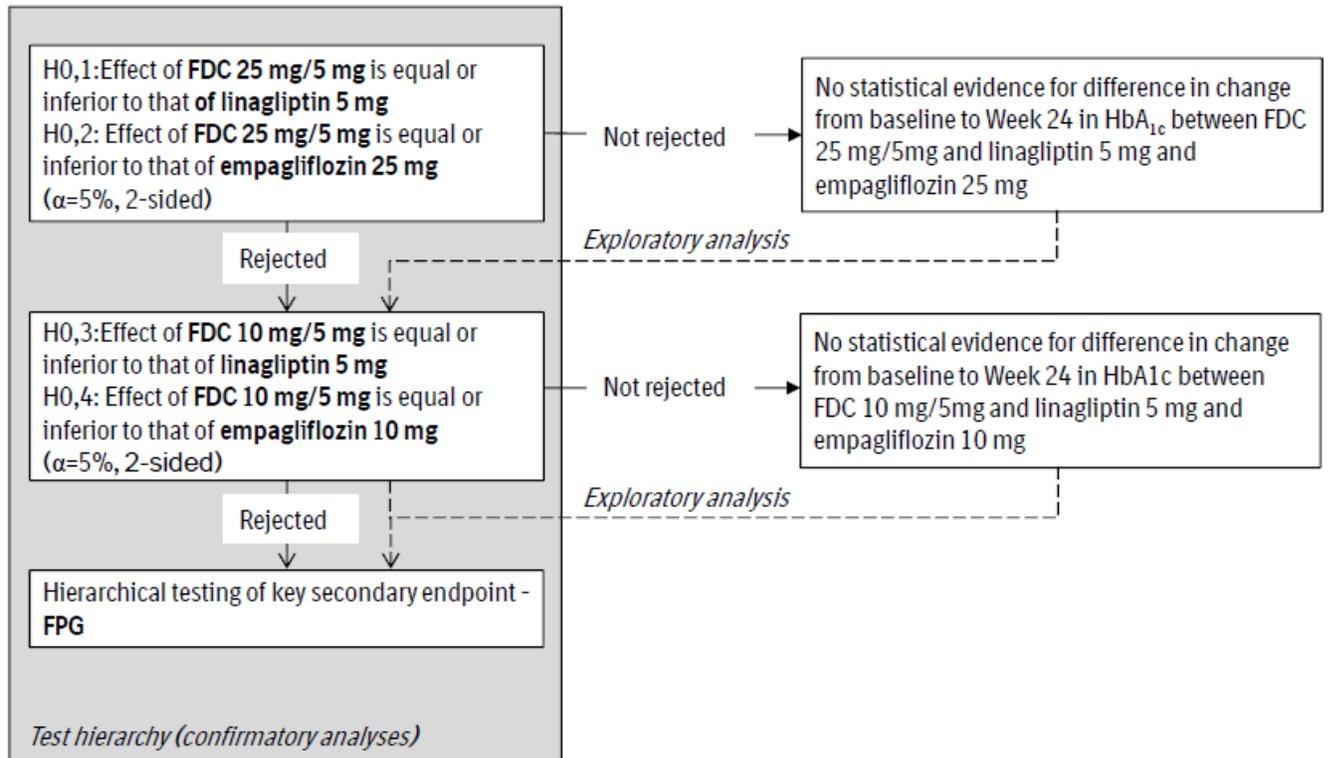
3. Occurrence of treat to target efficacy response: HbA1c of <7.0% (<53.0 mmol/mol) after 24 weeks of treatment

Testing Hierarchy

A separate testing procedure was followed for each of the patient populations with the high dose of the FDC being tested first against each respective monotherapy. Given that these were

significant then the low FDC was tested against respective monotherapies. The testing hierarchy used for both the primary endpoint and first secondary endpoint of FPG is given in Figure 3.

Figure 3: Applicant created schematic for the Primary Endpoint Testing Hierarchy



Both null hypotheses had to be rejected with a 2-sided hypothesis test with $\alpha=0.05$ at each step before proceeding. If all primary endpoint hypotheses are significant, then the first key secondary endpoint of change in FPG could then be tested using the same hypothesis hierarchy. If all hypotheses were significant for FPG, then the testing hierarchy would continue with hypotheses for change in body weight. The following testing hierarchy was implemented for this secondary endpoint with a two-sided testing procedure setting α at 0.05.

1. H0,1: Effect of BI 10773 25 mg/linagliptin 5 mg is equal or inferior to that of linagliptin 5 mg;
Against the alternative HA,1: Effect of BI 10773 25 mg/linagliptin 5 mg is superior to linagliptin 5 mg.
2. H0,2: Effect of BI 10773 10 mg/linagliptin 5 mg is equal or inferior to that of linagliptin 5 mg;
Against alternative HA,2: Effect of BI 10773 10 mg/linagliptin 5 mg is superior to linagliptin 5 mg.
3. H0,3: Effect of BI 10773 25 mg/linagliptin 5 mg is equal or inferior to that of BI 10773 25 mg;

Against the alternative HA,3: Effect of linagliptin 5 mg/BI 10773 25 mg is superior to BI 10773 25 mg.

4. H0,4: Effect of BI 10773 10 mg/linagliptin 5 mg is equal or inferior to that of BI 10773 10 mg;

Against the alternative HA,4: Effect of BI 10773 10 mg/linagliptin 5 mg is superior to BI 10773 10 mg.

The third secondary endpoint of treat-to-target efficacy response HbA1c<7% was tested last if all preceding hypotheses were significant. The following order was specified here for testing the dosages of FDC versus different monotherapies for this endpoint:

1. High dose FDC vs. linagliptin 5 mg
2. Low dose FDC vs. linagliptin 5 mg
3. High dose FDC vs. empagliflozin 25 mg
4. Low dose FDC vs. empagliflozin 10 mg

3.2.2 Statistical Methodologies

Metformin background and treatment naïve patients were treated as two independent patient populations in this study. ANCOVA with last observation carried forward (LOCF) was used on the full analysis set (FAS) with randomized treatment for the primary endpoint. The model included fixed effects for treatment, region, and also the covariates baseline HbA1c, and screening eGFR to measure renal function.

$$\text{HbA1c change from baseline} = \text{overall mean} + \text{baseline HbA1c} + \text{treatment} + \text{renal function} + \text{geographical region} + \text{random error}$$

In a TSAP submitted in response to advice given by the Agency after unblinding, the main analysis was changed to be an MMRM. Due to the fact that both methods impute data based on data observed before dropout, meaning results will be similar, and ANCOVA was pre-specified, this review focuses on results from the ANCOVA. Renal function was measured through a bivariate eGFR score of <90 or at least 90.

The MMRM analysis for treatment comparison of the adjusted mean change in HbA1c from baseline at Week 24 was originally specified as a REML based sensitivity analysis using the same population specified for ANCOVA (later changed to be the main analysis method in the TSAP). An unstructured covariance was to be used unless it failed to converge, in which case the following covariance structures were to be implemented with the best model used in the primary analysis as determined by AIC: unstructured, compound symmetry, variance components, and Toeplitz. The model for the MMRM analysis was,

$$\text{HbA1c change from baseline} = \text{overall mean} + \text{baseline HbA1c} + \text{treatment} + \text{screening eGFR} + \text{region} + \text{visit} + \text{visit by treatment interaction} + \text{random error.}$$

Other sensitivity analyses for the primary endpoint used the 24 week and 52 week FAS completers and PPS populations in order to assess the impact protocol violations and premature discontinuation had on the model used in the primary analysis. For my own analysis, I tested all

possible combinations of treatments (not just the ones specified by the sponsor) in order to gain a better understanding of where higher doses and combination therapy could be an improvement over low doses and monotherapies. Since the study was not designed for these hypotheses, only results that seemed relevant to better understanding the FDC are discussed.

Once all the hypotheses in the primary endpoint hierarchy, described earlier, were found to be significant, the key secondary endpoint of fasting plasma glucose (FPG) was then specified to be tested using the same hierarchy. A similar ANCOVA model but with an additional baseline FPG covariate (baseline HbA1c also stayed in the model).

If this set of FPG hypotheses were found to be significant, then the set of hypotheses specified for body weight could then be tested. Again, a similar ANCOVA model as specified for the primary endpoint was used also including an additional baseline weight covariate.

The last secondary endpoint that was tested was the treat-to-target endpoint (HbA1c < 7%) for four different hypotheses testing the FDC therapies against their respective monotherapies. Testing was done using a logistic regression, imputing all missing data as failures. The model for this regression was similar to the ANCOVA model with factors for treatment, baseline renal function, geographical region, and a baseline HbA1c covariate. Reported odds ratios along with 95% CIs and p-values were based on this model.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Metformin Treated Subjects

In the study report the applicant states that there were 1179 subjects enrolled with 747 entering in the placebo run-in period. Of these, 686 were randomized in a 1:1:1:1:1 ratio to the study arms with:

- 137 on empagliflozing 25 mg/linagliptin 5 mg,
- 136 on empagliflozin 10 mg/linagliptin 5 mg,
- 141 on empagliflozing 25 mg,
- 140 on empagliflozin 10 mg,
- 132 on linagliptin 5 mg.

They found 628/686 (92.5%) completed the 24-week treatment period for the primary analysis with 58 (8.5%) prematurely discontinuing trial medication. Of these, 17 subject (2.5%) discontinued due to adverse events, 15 (2.2%) were lost to follow-up. For my own analysis, the proportion of dropouts in the dataset over time are shown in Figure 4. Table 4 contains descriptive statistics for the baseline characteristics in the study. It should be noted that the sample size that I used for the descriptive analysis and what was stated in the study report differ. In staying with the ITT principle I used all randomized subjects in the original dataset for the purposes of the descriptive analysis. The proportions were ultimately the same and appear to be balanced between the five arms.

Figure 4: Proportion of missing data at each visit for the metformin treated population

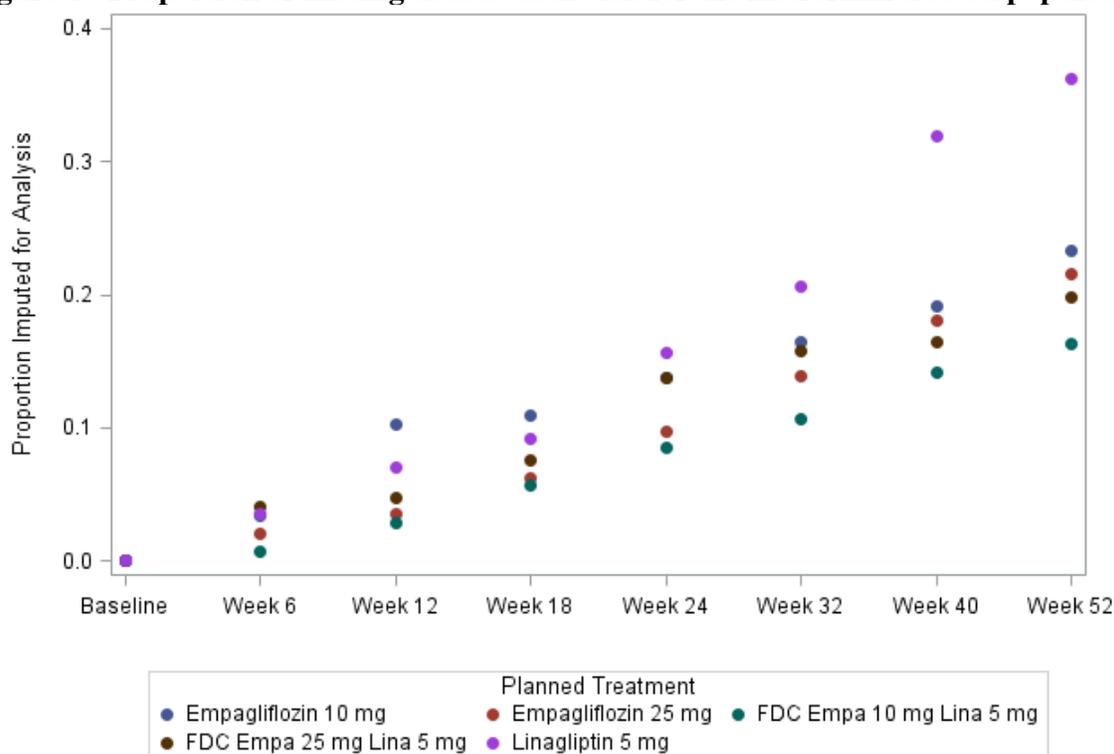


Table 4: Descriptive Statistics for the Metformin Treated Population

Characteristic	Category	Empa 25 mg	Empa 10 mg	Empa 25 mg	Empa 10 mg	Lina 5 mg
		Lina 5 mg (N=146)	Lina 5 mg (N=141)	(N=144)	(N=146)	(N=141)
Sex	Female	66 (45.21%)	55 (39.01%)	76 (52.78%)	62 (42.47%)	69 (48.94%)
	Male	80 (54.79%)	86 (60.99%)	68 (47.22%)	84 (57.53%)	72 (51.06%)
Race	White	105 (71.92%)	107 (75.89%)	103 (71.53%)	110 (75.34%)	103 (73.05%)
	Black / African American	11 (7.53%)	13 (9.22%)	14 (9.72%)	11 (7.53%)	14 (9.93%)
	Asian	22 (15.07%)	18 (12.77%)	20 (13.89%)	19 (13.01%)	15 (10.64%)
	American Indian / Alaska Native	8 (5.48%)	3 (2.13%)	7 (4.86%)	6 (4.11%)	9 (6.38%)
Ethnicity	Hispanic / Latino	42 (28.77%)	37 (26.24%)	41 (28.47%)	52 (35.62%)	48 (34.04%)
	Not Hispanic / Latino	104 (71.23%)	104 (73.76%)	103 (71.53%)	94 (64.38%)	93 (65.96%)
Region	North America	68 (46.58%)	69 (48.94%)	69 (47.92%)	71 (48.63%)	67 (47.52%)
	Latin America	19 (13.01%)	18 (12.77%)	20 (13.89%)	19 (13.01%)	18 (12.77%)

	Europe	39 (26.71%)	37 (26.24%)	37 (25.69%)	39 (26.71%)	39 (27.66%)
	Asia	20 (13.70%)	17 (12.06%)	18 (12.50%)	17 (11.64%)	17 (12.06%)
Age Categories	<50 years	31 (21.23%)	32 (22.70%)	40 (27.78%)	39 (26.71%)	39 (27.66%)
	50 to <65 years	79 (54.11%)	82 (58.16%)	78 (54.17%)	80 (54.79%)	72 (51.06%)
	65 to <75 years	32 (21.92%)	22 (15.60%)	22 (15.28%)	20 (13.70%)	27 (19.15%)
	at least 75 years	4 (2.74%)	5 (3.55%)	4 (2.78%)	7 (4.79%)	3 (2.13%)
Time since diagnosis of T2DM	≤ 1 Year	11 (7.53%)	19 (13.48%)	10 (6.94%)	13 (8.90%)	10 (7.09%)
	>1 to 5 Years	50 (34.25%)	50 (35.46%)	51 (35.42%)	56 (38.36%)	54 (38.30%)
	>5 to 10 Years	52 (35.62%)	45 (31.91%)	52 (36.11%)	41 (28.08%)	45 (31.91%)
	>10 Years	33 (22.60%)	27 (19.15%)	31 (21.53%)	36 (24.66%)	32 (22.70%)
Baseline eGFR (MDRD)	.	2 (1.37%)	3 (2.13%)	0 (0.00%)	0 (0.00%)	2 (1.42%)
	at least 90 mL/min/1.73m ²	64 (43.84%)	62 (43.97%)	62 (43.06%)	71 (48.63%)	60 (42.55%)
	60 to 90 mL/min/1.73m ²	78 (53.42%)	75 (53.19%)	80 (55.56%)	69 (47.26%)	72 (51.06%)
	30 to 60 mL/min/1.73m ²	2 (1.37%)	1 (0.71%)	2 (1.39%)	6 (4.11%)	7 (4.96%)
HbA1c at Baseline	<8%	84 (57.53%)	80 (56.74%)	75 (52.08%)	87 (59.59%)	77 (54.61%)
	8% to <9%	38 (26.03%)	42 (29.79%)	50 (34.72%)	38 (26.03%)	43 (30.50%)
	at least 9%	24 (16.44%)	19 (13.48%)	19 (13.19%)	21 (14.38%)	21 (14.89%)
Metformin at Baseline	Dose<1500 mg	16 (10.96%)	3 (2.13%)	8 (5.56%)	7 (4.79%)	9 (6.38%)
	Dose at least 1500 mg	130 (89.04%)	138 (97.87%)	136 (94.44%)	139 (95.21%)	132 (93.62%)
Weight at Baseline	N	146	141	144	146	141
	Mean (SD)	85.3 (20)	86.1 (19)	88.5 (18.3)	85.9 (18.3)	85.4 (19)
	Median (Min, Max)	82.6 (48.9, 141.1)	84.8 (39, 143.1)	87 (50, 146.3)	85.5 (43.9, 130)	85.2 (46.8, 145)
BMI at Baseline	N	146	141	144	146	141
	Mean (SD)	30.5 (5.5)	30.8 (5.6)	32.1 (5.4)	30.9 (5.4)	30.6 (5.6)
	Median (Min, Max)	29.3 (20.5, 44.9)	29.9 (19.1, 44)	31.7 (17.9, 43.7)	30.4 (16.7, 49.8)	30.5 (18.6, 44.3)
SBP at Baseline	N	146	140	144	146	141
	Mean (SD)	130.5 (15.6)	129.5 (14.8)	128.3 (13.5)	130.7 (14)	128.5 (12.8)
	Median (Min, Max)	130 (96, 180)	130 (98, 180)	127 (102, 182)	130 (92, 166)	130 (96, 178)
DBP at Baseline	N	146	140	144	146	141

Mean (SD)	78.2 (9.1)	78.3 (8.3)	79.3 (8.8)	79.7 (10)	77.3 (8.7)
Median (Min, Max)	78 (52, 106)	80 (60, 100)	80 (55, 109)	80 (51, 109)	78 (52, 100)

Treatment naïve subjects

The study report indicated that there were 1325 enrolled treatment naïve patients with 757 starting the placebo run-in period. Using the same 1:1:1:1:1 ratio 677 patients were randomized in this group. There were 614 of the 677 treatment naïve subjects (90.7%) that completed the 24-week treatment period for the primary analysis. There were 63 (9.3%) who prematurely discontinued with the most common reason for discontinuation being an adverse event (20, 3%). Recruitment took place in 201 centers across 22 countries in North America (46.3%), Europe (25.3%), Latin America (17.7%), and Asia (10.8%). There were 570/677 (84.2%) that completed the full 52-week treatment period with adverse events being the reported reason for discontinuation in 31 (4.6%) patients followed by 26 (3.8%) lost to follow-up. The proportion of dropouts that I found at each visit for the full dataset is shown below in Figure 5. Table 5 contains baseline descriptive statistics for the ITT naïve population.

Figure 5: Proportion of Missing Data at each visit for the Treatment Naïve Population

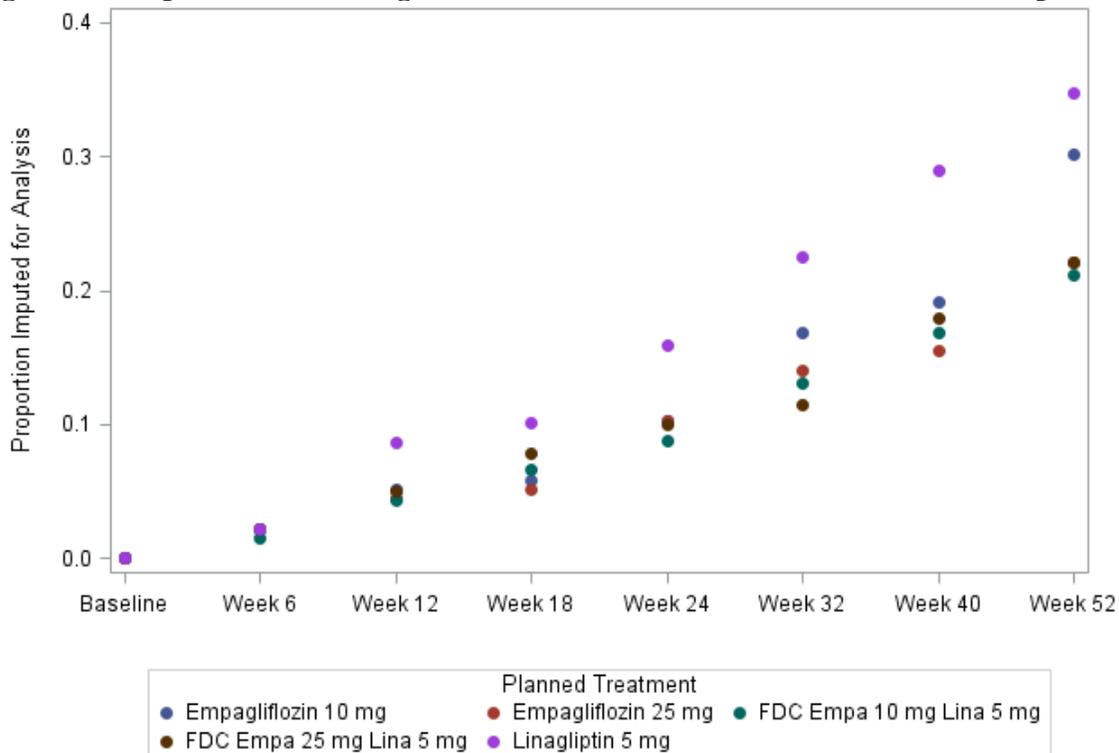


Table 5: Baseline Descriptive Statistics for the Treatment Naive Population

Characteristic	Category	Empa 25 mg	Empa 10 mg	Empa 25 mg	Empa 10 mg	Lina 5 mg
		Lina 5 mg (N=139)	Lina 5 mg (N=137)	(N=136)	(N=137)	(N=138)
Sex	Female	65 (46.76%)	63 (45.99%)	57 (41.91%)	71 (51.82%)	61 (44.20%)
	Male	74 (53.24%)	74 (54.01%)	79 (58.09%)	66 (48.18%)	77 (55.80%)
Race	.	0 (0.00%)	1 (0.73%)	0 (0.00%)	1 (0.73%)	0 (0.00%)
	White	109 (78.42%)	102 (74.45%)	94 (69.12%)	104 (75.91%)	107 (77.54%)
	Black / African American	9 (6.47%)	12 (8.76%)	11 (8.09%)	9 (6.57%)	6 (4.35%)
	Asian	12 (8.63%)	14 (10.22%)	20 (14.71%)	13 (9.49%)	17 (12.32%)
	American Indian / Alaska Native	9 (6.47%)	8 (5.84%)	11 (8.09%)	10 (7.30%)	8 (5.80%)
Ethnicity	Hispanic / Latino	48 (34.53%)	47 (34.31%)	44 (32.35%)	49 (35.77%)	44 (31.88%)
	Not Hispanic / Latino	91 (65.47%)	90 (65.69%)	92 (67.65%)	88 (64.23%)	94 (68.12%)
Region	North America	58 (41.73%)	57 (41.61%)	56 (41.18%)	57 (41.61%)	58 (42.03%)
	Latin America	28 (20.14%)	31 (22.63%)	30 (22.06%)	32 (23.36%)	29 (21.01%)
	Europe	36 (25.90%)	35 (25.55%)	33 (24.26%)	34 (24.82%)	34 (24.64%)
	Asia	17 (12.23%)	14 (10.22%)	17 (12.50%)	14 (10.22%)	17 (12.32%)
Age Categories	<50 years	44 (31.65%)	34 (24.82%)	32 (23.53%)	42 (30.66%)	41 (29.71%)
	50 to <65 years	70 (50.36%)	78 (56.93%)	83 (61.03%)	75 (54.74%)	73 (52.90%)
	65 to <75 years	24 (17.27%)	23 (16.79%)	19 (13.97%)	18 (13.14%)	22 (15.94%)
	at least 75 years	1 (0.72%)	2 (1.46%)	2 (1.47%)	2 (1.46%)	2 (1.45%)
Time since diagnosis of T2DM	≤ 1 Year	42 (30.22%)	46 (33.58%)	48 (35.29%)	44 (32.12%)	50 (36.23%)
	>1 to 5 Years	55 (39.57%)	48 (35.04%)	49 (36.03%)	62 (45.26%)	59 (42.75%)
	>5 to 10 Years	29 (20.86%)	31 (22.63%)	26 (19.12%)	15 (10.95%)	24 (17.39%)
	>10 Years	13 (9.35%)	12 (8.76%)	13 (9.56%)	16 (11.68%)	5 (3.62%)
Baseline eGFR (MDRD)	.	3 (2.16%)	1 (0.73%)	1 (0.74%)	4 (2.92%)	1 (0.72%)
	at least 90 mL/min/1.73m ²	65 (46.76%)	55 (40.15%)	61 (44.85%)	61 (44.53%)	61 (44.20%)
	60 to 90 mL/min/1.73m ²	67 (48.20%)	77 (56.20%)	72 (52.94%)	69 (50.36%)	76 (55.07%)
	30 to 60 mL/min/1.73m ²	4 (2.88%)	4 (2.92%)	2 (1.47%)	3 (2.19%)	0 (0.00%)
HbA1c at Baseline	<8%	76 (54.68%)	69 (50.36%)	74 (54.41%)	74 (54.01%)	71 (51.45%)
	8% to <9%	40 (28.78%)	44 (32.12%)	35 (25.74%)	33 (24.09%)	44 (31.88%)
	at least 9%	23 (16.55%)	24 (17.52%)	27 (19.85%)	30 (21.90%)	23 (16.67%)

	N	139	137	136	137	138
Weight at Baseline	Mean (SD)	88.3 (18.4)	87.5 (18.4)	86.5 (19.6)	87.9 (23.6)	89.2 (19.9)
	Median (Min, Max)	87 (50.8, 137)	87.7 (43.4, 138.6)	83.1 (50.1, 155.6)	82.6 (47.6, 173.8)	88.5 (39, 153.8)
	N	139	137	136	137	138
BMI at Baseline	Mean (SD)	31.9 (5.3)	31.6 (5.5)	31 (5.7)	31.5 (5.6)	31.8 (5.9)
	Median (Min, Max)	31.2 (20.1, 43.8)	31.1 (20.6, 44.2)	30.3 (20.2, 45)	30.5 (21.4, 44.8)	30.7 (17.3, 44.9)
	N	139	137	136	136	138
SBP at Baseline	Mean (SD)	127.6 (14.8)	126.3 (14.2)	128.4 (14.9)	127.5 (15.6)	126.1 (14.5)
	Median (Min, Max)	127 (97, 178)	126 (91, 170)	126 (95, 190)	126 (90, 196)	125 (87, 170)
	N	139	137	136	136	138
DBP at Baseline	Mean (SD)	77.6 (9)	78 (8.8)	78.2 (9)	78.6 (8.6)	77.3 (9.2)
	Median (Min, Max)	77 (58, 102)	78 (50, 98)	78 (52, 104)	79 (57, 106)	78 (56, 101)

3.2.4 Results and Conclusions

The type I error testing hierarchy for the primary endpoint in this trial specified that separate testing procedures were to be run on the primary endpoint of HbA1c reduction at 24 weeks for high dose combination (Empa 25mg / Lina 5mg) against each monotherapy. Both null hypotheses had to be rejected before proceeding to testing low dose combination (Empa 10mg / Lina 5mg) against its respective monotherapies. Given that was significant, then hierarchical testing procedures could be implemented for secondary endpoints.

3.2.4.1 Metformin Treated Subjects Results

Primary Endpoint Results

Table 6 shows the raw and adjusted HbA1c values at 24 weeks for the metformin treated population. There is a significant difference in HbA1c for those on the FDC versus monotherapy, all pre-specified ANCOVA results in the metformin group were significant with $p < 0.0001$ for the primary endpoint.

Table 6: Mean HbA1c Results for Metformin Treated Subjects

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=141	Empa 10 n=140	Lina 5 n=132
Mean HbA1c at Baseline	7.9	8	8	8	8
Mean HbA1c at Week 24	6.8	6.9	7.4	7.3	7.3
Mean Change from Baseline in HbA1c	-1.1	-1	-0.6	-0.7	-0.7
Adjusted change from Baseline in HbA1c (Mean, SE)	-1.2 (0.1)	-1.1 (0.1)	-0.7 (0.1)	-0.7 (0.1)	-0.8 (0.1)

Model based adjusted change from baseline included adjustment for baseline HbA1c, renal function, and region

The adjusted model based estimates for the differences between treatment arms in the primary endpoint are given in Table 7 with highlighted cells for the pre-specified hypotheses in the testing hierarchy. The results indicate a statistically significant difference between each of the FDCs against each of their respective monotherapies.

Table 7: Primary Endpoint Adjusted Differences between Treatments for Metformin Subjects

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-0.1 (-0.3, 0.1) 0.215				
Empa 25	-0.6 (-0.7, -0.4) <.0001	-0.4 (-0.6, -0.3) <.0001			
Empa 10	-0.5 (-0.7, -0.4) <.0001	-0.4 (-0.6, -0.2) <.0001	0.03 (-0.1, 0.2) 0.7352		
Lina 5	-0.5 (-0.7, -0.3) <.0001	-0.4 (-0.5, -0.2) <.0001	0.1 (-0.1, 0.2) 0.4207	0.04 (-0.1, 0.2) 0.6376	

Although not pre-specified in the protocol, it does remain relevant to check whether there are any efficacy differences between the varying dose levels of the FDC treatment. The difference between the high FDC and low FDC remains less pronounced and non-significant (p=0.22) in this population.

Secondary Endpoint Results, Change in Fasting Plasma Glucose

Since results for the primary endpoint were significant in this population, it was appropriate to continue in the testing hierarchy with the endpoints for change from baseline in fasting plasma glucose (FPG). Differences from baseline for this endpoint between treatment arms are fairly pronounced as can be seen in Table 8. The adjusted estimates of these differences along with hypothesis test results seen in Table 9 are all significant when testing each FDC against monotherapies. However, we continue to see a non-significant difference between the high and low dose FDC. Since this was not a pre-specified hypothesis, it will remain a clinical question as to whether any difference we do see justifies the higher dosage.

Table 8: Mean FPG Results for Metformin Treated Subjects

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=141	Empa 10 n=140	Lina 5 n=132
Mean FPG at Baseline	154.5	156.5	160	162.1	155.8
Mean FPG at Week 24	121.7	125.8	141	139.6	144
Mean Change from Baseline in FPG	-30.9	-30.9	-19.3	-22.5	-12
Adjusted change in FPG (Mean, SE)	-36.6 (2.6)	-33.9 (2.6)	-20.4 (2.6)	-22.4 (2.6)	-15.1 (2.6)

Adjusted for baseline HbA1c., baseline FPG, geography, and renal function

Table 9: FPG Differences between Treatment Arms for Metformin Treated Subjects

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-2.7 (-9.7, 4.3) 0.4442				
Empa 25	-16.2 (-23.2, -9.3) <.0001	-13.5 (-20.4, -6.6) 0.0001			
Empa 10	-14.3 (-21.2, -7.3) <.0001	-11.6 (-18.5, -4.6) 0.0012	2 (-4.9, 8.9) 0.5744		
Lina 5	-21.5 (-28.6, -14.5) <.0001	-18.8 (-25.9, -11.8) <.0001	-5.3 (-12.3, 1.7) 0.1376	-7.3 (-14.3, -0.2) 0.0425	

Secondary Endpoint Results, Change in Body Weight

Proceeding with the testing hierarchy, we can now examine results relating to change in body weight. The changes in body weight look to be somewhat similar in the FDC and empagliflozin treatment arms. Table 11 shows model adjusted differences between the arms with statistically significant differences only seen when comparing each treatment arm with linagliptin 5mg. The nature of the testing hierarchy is somewhat different for this endpoint which allows the applicant to claim superiority here for both low and high dose FDC against linagliptin. However, we fail to see statistically significant differences in each of the FDCs when compared with their empagliflozin monotherapy counterparts. (b) (4)

Table 10: Mean Body Weight Results for Metformin Treated Subjects

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=141	Empa 10 n=140	Lina 5 n=132
Mean Weight at Baseline	85.3	86.4	87.8	85.7	85.4
Mean Weight at Week 24	82.4	83.8	84.9	83.2	84.6
Mean Change from Baseline in Weight	-2.9	-2.6	-2.9	-2.4	-0.7
Adjusted change in Weight (Mean, SE)	-3.1 (0.3)	-2.8 (0.3)	-3.1 (0.3)	-2.7 (0.3)	-1 (0.3)

Adjusted for baseline HbA1c, baseline FPG, geography, and renal function

Table 11: Change in Body Weight Differences between Treatment Arms, Metformin

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-0.3 (-1, 0.4) 0.348				
Empa 25	-0.1 (-0.8, 0.6) 0.8359	0.3 (-0.4, 1) 0.4603			
Empa 10	-0.5 (-1.2, 0.2) 0.1822	-0.1 (-0.8, 0.6) 0.6974	-0.4 (-1.1, 0.3) 0.2565		
Lina 5	-2.2 (-2.9, -1.5) <.0001	-1.9 (-2.6, -1.1) <.0001	-2.1 (-2.8, -1) <.0001	-1.7 (-2.4, -1) <.0001	

Secondary Endpoint Results, Treat to Target Efficacy Response HbA1c<7%

Results for the treat to target efficacy response of having an HbA1c under 7% are shown in Table 12 and Table 13. These results should be viewed simply as descriptive because hypotheses higher within the testing hierarchy were not significant. Since this endpoint is based on the primary endpoint of HbA1c, the results here provide further insight on how well subjects within each treatment are performing when compared with other treatments. There is an appreciable difference in the proportion of subjects achieving this endpoint in the FDC compared to the monotherapies as seen in Table 12. Odds ratios indicate a significantly greater odds, ranging from three to four, for achieving HbA1c<7% on a FDC than with a comparable monotherapy. We again see a non-significant difference between the low and high FDCs (p=0.48).

Table 12: Proportion of Subjects with HbA1c<7% in the Metformin Treated Subjects

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=141	Empa 10 n=140	Lina 5 n=132
HbA1c <7% at Baseline, n (%)	12 (8.8)	7 (5.2)	8 (5.7)	12 (8.6)	9 (6.8)
HbA1c <7% at Week 24, n (%)	88 (64.2)	81 (59.6)	51 (36.2)	47 (33.6)	50 (37.9)

Table 13: Odds Ratios between Treatment Arms for HbA1c<7%, Metformin

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	1.2 (0.7, 2.2) 0.4778				
Empa 25	4.1 (2.3, 7.3) <.0001	3.3 (1.9, 5.8) <.0001			
Empa 10	5.3 (2.9, 9.7) <.0001	4.3 (2.4, 7.7) <.0001	1.3 (0.7, 2.3) 0.3602		
Lina 5	3.9 (2.2, 7.1) <.0001	3.2 (1.8, 5.7) <.0001	1 (0.5, 1.7) 0.9142	0.7 (0.4, 1.3) 0.3113	

3.2.4.2 Treatment Naïve Subjects Results**Primary Endpoint Results**

Table 14 shows the raw and adjusted HbA1c values at 24 weeks for the treatment naïve population in this study. Table 15 contains testing estimates for differences between treatment arms and p-values using the ANCOVA model with a LOCF imputation. Highlighted values in the table were the pre-specified hypotheses in the testing hierarchy.

Table 14: Mean HbA1c Results for Treatment Naïve Subjects

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
Mean HbA1c at Baseline	8	8.1	8	8	8.1
Mean HbA1c at Week 24	6.9	6.8	7.1	7.2	7.4
Mean Change from Baseline in HbA1c	-1	-1.2	-0.9	-0.8	-0.7
Adjusted change in HbA1c (Mean, SE)	-1.1 (0.1)	-1.3 (0.1)	-1 (0.1)	-0.9 (0.1)	-0.7 (0.1)

Model based adjusted change from baseline included adjustment for baseline HbA1c, renal function, and region

Table 15: Primary Endpoint Adjusted Differences between Treatments, Treatment Naïve

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	0.2 (-0.05, 0.3) 0.1348				
Empa 25	-0.1 (-0.3, 0.1) 0.1775	-0.3 (-0.5, -0.1) 0.0046			
Empa 10	-0.3 (-0.5, -0.1) 0.0112	-0.4 (-0.6, -0.2) <.0001	-0.1 (-0.3, 0.1) 0.2333		
Lina 5	-0.4 (-0.6, -0.2) <.0001	-0.6 (-0.8, -0.4) <.0001	-0.3 (-0.5, -0.1) 0.0053	-0.2 (-0.4, 0.03) 0.1106	

Based on these results, it appears that the high FDC fails to demonstrate a significantly different change in HbA1C when compared with empagliflozin 25mg monotherapy. The low FDC did seem to have efficacy improvements over empagliflozin 10mg monotherapy and linagliptin monotherapy, but because the high FDC failed for the co-primary endpoints, the results for low FDC are considered exploratory. With a non-significant difference of 0.2 in the HbA1c primary endpoint in favor of the lower FDC, results in these tables also indicate there is the possibility that the lower dose combination could actually have a better effect on lowering HbA1c values than the higher dose in the treatment naïve population.

While it fails to demonstrate a significant difference from empagliflozin 25mg (p=0.18), the high dose combination may have a marginally significant effect when compared to low dose empagliflozin as monotherapy (this result should be interpreted with caution as it was neither pre-specified nor is there a multiplicity adjustment in place for it) as well as linagliptin 5mg.

The low dose combination does appear to be significantly better than both low dose monotherapies (p<.0001). Even when using a conservative Bonferroni adjustment for type I error these results remain significant. However, according to the structure of the testing hierarchy, these results are not considered significant for the pre-specified efficacy analysis.

In a sense, this section of the clinical trial for treatment naïve subjects was unsuccessful since results for the primary endpoint were non-significant. The consequences of this breakdown will be taken into account when considering all of the statistical outcomes and conclusions drawn for this population.

Week 52 Primary Endpoint Results for Treatment Naïve Subjects

Since results at the 24 week primary endpoint were suggestive of little to no difference in HbA1c change, I ran the same procedures at 52 weeks to see if this could provide a more comprehensive understanding of how the FDC works. It should be noted that at 52 weeks approximately 26% of the data were imputed with the most missing data coming from the low dose monotherapies.

The raw and adjusted mean HbA1c results at week 52 are given in Table 16 along with associated ANCOVA results in Table 17 running all pairwise comparisons.

Table 16: Mean HbA1c at 52 Weeks

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
Mean HbA1c at Baseline	8	8.1	8	8	8.1
Mean HbA1c at Week 24	6.8	6.8	7	7.2	7.5
Mean Change from Baseline in HbA1c	-1.1	-1.2	-1	-0.8	-0.5
Adjusted change in HbA1c (Mean, SE)	-1.2 (0.1)	-1.3 (0.1)	-1.1 (0.1)	-0.9 (0.1)	-0.6 (0.1)

Model based adjusted change from baseline included adjustment for baseline HbA1c, renal function, and region

Table 17: HbA1c Adjusted Differences at 52 Weeks between Treatments, Treatment Naive

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	0.05 (-0.2, 0.3) 0.6738				
Empa 25	-0.2 (-0.4, 0.1) 0.1836	-0.2 (-0.4, 0.03) 0.0808			
Empa 10	-0.3 (-0.6, -0.1) 0.006	-0.4 (-0.6, -0.1) 0.0016	-0.2 (-0.4, 0.1) 0.1546		
Lina 5	-0.7 (-0.9, -0.4) <.0001	-0.7 (-0.9, -0.5) <.0001	-0.5 (-0.7, -0.3) <.0001	-0.3 (-0.6, -0.1) 0.0054	

We see results similar to that of the 24 week analysis with high FDC still not statistically different from the high dose monotherapy for empagliflozin 25mg (p=0.18), nor does it show a difference from the low dose FDC (p=0.67). While low dose FDC appears to show superiority when compared to each of its monotherapy components, it remains uncertain if high dose FDC has the same level of increased efficacy when compared to monotherapy or even the low FDC.

Secondary Endpoint Results, Change in Fasting Plasma Glucose

Results for fasting plasma glucose (FPG) in the treatment naïve population are presented here but should be viewed as descriptive since we are no longer under the testing hierarchy. Results from Table 18 and Table 19 indicate differences in both FDC dosages when compared with linagliptin. However, we fail to see any differences between either the low or high FDC when compared with their respective empagliflozin monotherapies. Based on these results, there does not seem to be any additional benefit for FPG when using a combination therapy with linagliptin versus just using empagliflozin.

Table 18: Mean FPG for Treatment Naive Subjects

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
Mean FPG at Baseline	155.7	157.4	152	159.9	155.7
Mean FPG at Week 24	126.6	129.1	130	137.4	150.3
Mean Change from Baseline in FPG	-29.1	-28.2	-22	-22.5	-5.4
Adjusted change in FPG (Mean, Std Err)	-30.5 (2.8)	-29 (2.8)	-25.3 (2.8)	-21.7 (2.8)	-6.7 (2.8)

Adjusted for baseline HbA1c, baseline FPG, geography, and renal function

Table 19: FPG Differences between Treatment Arms, Treatment Naive

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-1.6 (-9.1, 6) 0.6729				
Empa 25	-5.2 (-12.7, 2.4) 0.1803	-3.6 (-11.2, 4) 0.359			
Empa 10	-8.9 (-16.5, -1.3) 0.0227	-7.3 (-14.9, 0.3) 0.0631	-3.7 (-11.3, 3.9) 0.3472		
Lina 5	-23.8 (-31.3, -16.2) <.0001	-5.2 (-12.7, 2.4) <.0001	-18.5 (-26.1, -11) <.0001	-14.8 (-22.4, -7.2) 0.0001	

Secondary Endpoint Results, Change in Body Weight

Efficacy results for change in body weight in the treatment naïve population are given in Table 20 and Table 21 for descriptive purposes in further detailing efficacy for the FDC when compared with monotherapy. We again see no evidence that either FDC provides any added efficacy benefit from adding linagliptin when compared with equal dosages of empagliflozin monotherapy.

Table 20: Mean Body Weight for Treatment Naive Subjects

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
Mean Weight at Baseline	88.4	87.4	86.6	87.8	89.3
Mean Weight at Week 24	86.4	84.7	84.4	85.5	88.4
Mean Change from Baseline in Weight	-2	-2.7	-2.2	-2.3	-0.9
Adjusted change in Weight (Mean, SE)	-2.1 (0.4)	-2.8 (0.4)	-2.3 (0.4)	-2.5 (0.4)	-0.9 (0.4)

Adjusted for baseline HbA1c., baseline FPG, geography, and renal function

Table 21: Body Weight differences between Treatment Arms, Treatment Naive

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	0.7 (-0.3, 1.7) 0.1575				
Empa 25	0.2 (-0.8, 1.2) 0.6609	-0.5 (-1.5, 0.5) 0.3309			
Empa 10	0.4 (-0.6, 1.4) 0.4706	-0.3 (-1.3, 0.6) 0.4916	0.1 (-0.8, 1.1) 0.7775		
Lina 5	-1.2 (-2.2, -0.2) 0.0195	-1.9 (-2.9, -0.9) 0.0002	-1.4 (-2.4, -0.4) 0.0058	-1.5 (-2.5, -0.5) 0.0024	

Secondary Endpoint Results, Treat to Target Efficacy Response HbA1c<7%

The treat to target efficacy endpoint of HbA1c<7% can serve to give us a better understanding of how the failed portions of the primary endpoint change in HbA1c levels fared when examined as a binary outcome. Results in Table 22 show the number and proportion of subjects in each treatment arm with HbA1c under 7%. Table 23 contains adjusted odds ratios for this endpoint. With an odds ratio of almost two in favor of high FDC versus empagliflozin 25 monotherapy (this comparison in the primary outcome of continuous HbA1c failed to show any difference), we see some suggestion that the FDC could almost double the odds of achieving a HbA1c level below 7%. These findings should be viewed lightly, keeping in mind that many previous endpoints higher in the hierarchy have already failed in this population.

Table 22: Treatment Naive Subjects with HbA1c<7%

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
HbA1c <7% at Baseline, n (%)	12 (9)	13 (9.6)	16 (11.9)	12 (9)	6 (4.4)
HbA1c <7% at Week 24, n (%)	79 (57.7)	88 (64.7)	60 (44.4)	58 (43.3)	45 (33.3)

Table 23: Adjusted ORs for HbA1c<7%, Treatment Naive

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	0.7 (0.4, 1.1) 0.1316				
Empa 25	1.9 (1.1, 3.2) 0.0182	2.8 (1.7, 4.8) 0.0001			
Empa 10	1.9 (1.1, 3.2) 0.0177	2.8 (1.7, 4.9) 0.0001	1 (0.6, 1.7) 0.9818		
Lina 5	3 (1.7, 5) <.0001	4.5 (2.6, 7.7) <.0001	1.6 (0.9, 2.7) 0.088	1.6 (0.9, 2.7) 0.0946	

Adjusted for baseline HbA1c, geography, and renal function

3.2.4.3 Comparing High and Low FDC

Since the question of whether the efficacy for the higher FDC is statistically better than the lower FDC came up during the process of this review, it seemed relevant to look into the matter further. This, however, was not a pre-specified hypothesis in the protocol. For this reason, it would seem practical to pool the two populations to further explore whether there is a statistically significant difference between the high and low FDC. The primary endpoint results for HbA1c, with negative differences favoring high FDC, yielded an adjusted difference between the two treatments of -0.11 (-0.28, 0.06) in the metformin subjects, as seen in Table 7, and 0.15 (-0.05, 0.35) in the treatment naïve subjects, as seen in Table 15. Since these non-significant results go in opposite directions we would not expect to see significant or more relevant pooled

results. Indeed, pooling these results, adjusting for stratification between the populations, yields a difference between treatments even closer to zero with tighter confidence intervals. There is a general lack of supportive evidence showing better efficacy for higher FDC when compared to low FDC in both populations.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroups for age, baseline HbA1c, BMI, baseline weight, geographical region, race, sex, ethnicity, time since diagnosis, renal impairment, history of hypertension, HOMA-IR, and HOMA-IS were pre-specified in the SAP. The same ANCOVA model specified for the primary endpoint was fit for each subgroup with an additional baseline and subgroup by treatment interaction. The subgroup interaction was specified to be significant if the p-value was below 0.1. Subgroup analyses were run separately and are presented in separate tables for the metformin and the treatment naïve populations.

4.1 Gender, Race, Age, and Geographic Region

Descriptive statistics for age, sex, race, and region are presented for the metformin treated subjects in Table 24, and for treatment naïve subjects in Table 25. Tests for interaction with treatment were run for each subgroup using the same baseline model specified for the primary endpoint analysis. No interaction terms were found to be significant for any of these subgroups.

Table 24: Subgroup Statistics for Change in HbA1c in Metformin Treated Subjects

		Empa25/Lina5		Empa10/Lina5		Empa 25		Empa 10		Lina 5	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age	<65	104	-1.2 (0.7)	111	-1 (0.9)	116	-0.7 (1.1)	114	-0.7 (0.8)	104	-0.7 (0.8)
	≥65	33	-0.9 (0.7)	25	-1 (0.7)	25	-0.5 (0.5)	26	-0.3 (0.6)	28	-0.8 (0.6)
Sex	Male	73	-1.1 (0.7)	84	-1.2 (0.9)	66	-0.8 (0.8)	81	-0.7 (0.8)	67	-0.8 (0.7)
	Female	64	-1.1 (0.8)	52	-0.8 (0.8)	75	-0.5 (1.2)	59	-0.6 (0.8)	65	-0.7 (0.8)
Race	White	99	-1.6 (0.7)	103	-1 (0.9)	101	-0.6 (1.1)	107	-0.6 (0.7)	97	-0.7 (0.7)
	Black	8	-0.9 (0.7)	12	-1 (0.8)	13	-0.7 (0.8)	8	-0.2 (0.7)	11	-0.9 (0.6)
	Asian	22	-1.1 (0.7)	18	-1.2 (0.9)	20	-0.8 (0.9)	19	-0.9 (0.9)	15	-0.9 (0.9)
	Other	8	-1.1 (0.3)	3	-1 (0.4)	7	-1 (1.4)	6	-1.3 (1)	9	-0.6 (0.6)
Region	North America	63	-1.1 (0.7)	65	-0.9 (0.9)	67	-0.5 (1.2)	67	-0.5 (0.8)	59	-0.4 (0.7)
	Latin America	19	-0.9 (0.6)	18	-1.4 (0.7)	20	-0.9 (1)	19	-0.9 (0.8)	18	-0.8 (0.7)
	Europe	40	-1.3 (0.8)	41	-1 (0.8)	43	-0.6 (0.7)	40	-0.7 (0.7)	44	-0.9 (0.6)
	Asian	15	-1.2 (0.7)	12	-1.4 (0.7)	11	-0.8 (1.1)	14	-0.9 (1.1)	11	-0.9 (1)

Table 25: Subgroup Statistics for Change in HbA1c in Treatment Naive Subjects

		Empa25/Lina5		Empa10/Lina5		Empa 25		Empa 10		Lina 5	
		N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)
Age	<65	113	-1.1 (1)	111	-1.3 (1)	114	-0.9 (1)	114	-0.8 (1)	111	-0.7 (1)
	≥65	24	-0.6 (0.7)	25	-1 (0.8)	21	-0.9 (1)	20	-0.8 (0.9)	24	-0.7 (1)
Sex	Male	72	-1.3 (1.1)	74	-1.2 (1)	78	-1 (1)	65	-0.8 (0.9)	75	-0.8 (0.9)
	Female	65	-0.8 (0.8)	62	-1.2 (0.9)	57	-0.8 (0.9)	69	-0.8 (0.9)	60	-0.6 (1)
Race	White	107	-1.1 (1)	101	-1.2 (1)	93	-0.9 (1)	101	-0.8 (0.9)	104	-0.6 (0.9)
	Black	9	-1.3 (0.7)	12	-1.2 (1)	11	-0.7 (1.3)	9	-1 (1.2)	6	-0.7 (1.4)
	Asian	12	-1 (1.2)	14	-1.6 (0.9)	20	-1.2 (0.9)	13	-0.8 (0.7)	17	-1 (1)
	Other	9	-0.7 (1.4)	9	-1.7 (0.9)	11	-0.6 (0.9)	11	-1.1 (0.8)	8	-0.6 (0.8)
Region	North America	57	-1.2 (0.9)	56	-1.2 (0.9)	56	-0.8 (1)	57	-0.7 (0.9)	58	-0.5 (0.9)
	Latin America	29	-1 (1.1)	31	-1.3 (0.9)	30	-1 (0.9)	31	-1 (1.1)	29	-0.7 (0.9)
	Europe	41	-0.9 (1)	39	-1.2 (1)	35	-0.9 (1.1)	36	-0.8 (0.9)	37	-0.7 (1)
	Asian	10	-1.1 (1.3)	10	-1.6 (1)	14	-1.1 (0.9)	10	-0.8 (0.6)	11	-1.2 (1)

4.2 Other Special/Subgroup Populations

Other subgroups specified by the applicant which were analyzed for both populations were Baseline HbA1c, BMI, baseline weight, ethnicity of Hispanic or Latino, time since diagnosis of type 2 diabetes mellitus, renal function, and hypertension. In the treatment naïve group baseline HOMA-IR and HOMA-IS were also analyzed. Descriptive results for these subgroups are shown in Table 26 and Table 27. It is well known that baseline HbA1c effects treatment differences seen over time, so the fact that we did find significant treatment interactions ($p < 0.1$) in both groups was not wholly unexpected.

Renal function was found to have a significant treatment interaction ($p < 0.1$) in the treatment naïve subjects. This finding confirms previous trial results for empagliflozin which also found significant treatment interaction with renal function. Only subjects with mild to moderate renal impairment were included in this study; further studies for this treatment designed with a focus on renal function would be necessary to draw any definitive conclusions on this treatment interaction.

Table 26: Other Subgroup Stats for Change in HbA1c in Metformin Treated Subjects

		Empa25/Lina5		Empa10/Lina5		Empa 25		Empa 10		Lina 5	
		N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)
Baseline HbA1c	<8.5	104	-0.9 (0.6)	105	-0.9 (0.7)	104	-0.4 (1)	106	-0.5 (0.6)	99	-0.6 (0.7)
	≥8.5	33	-1.8 (0.8)	31	-1.6 (1.2)	37	-1.2 (1)	34	-1.2 (1)	33	-1 (0.9)
BMI	<25	17	-1.1 (0.5)	20	-1.2 (0.9)	10	-0.5 (1)	16	-0.4 (0.7)	21	-0.8 (0.6)

	≥25	120	-1.1 (0.7)	116	-1 (0.8)	131	-0.6 (1)	124	-0.7 (0.8)	111	-0.7 (0.8)
Baseline Weight	≤70	30	-1.1 (0.6)	26	-1.1 (0.8)	24	-0.5 (0.9)	31	-0.7 (0.7)	32	-0.6 (0.5)
	70 to 80	35	-1.2 (0.8)	27	-1.3 (1)	22	-0.7 (0.9)	27	-0.8 (0.9)	21	-0.9 (0.9)
	80 to 90	26	-1 (0.8)	26	-0.8 (0.8)	34	-0.8 (0.8)	27	-0.8 (0.9)	26	-0.9 (0.8)
	>90	46	-1.1 (0.6)	57	-1 (0.8)	61	-0.5 (1.2)	55	-0.5 (0.7)	53	-0.6 (0.7)
Ethnicity	Hispanic/Latino	35	-1.1 (0.8)	32	-1.2 (0.9)	39	-0.6 (1.2)	46	-0.7 (0.9)	40	-0.5 (0.8)
	Not H/L	102	-1.2 (0.7)	104	-1 (0.8)	102	-0.6 (1)	94	-0.6 (0.8)	92	-0.8 (0.7)
Time since T2DM	≤1 Year	11	-1.2 (0.6)	19	-1.4 (0.7)	10	-0.7 (0.7)	13	-1 (0.9)	10	-0.8 (0.2)
	1 to 5 Years	47	-1.1 (0.7)	49	-1.1 (0.9)	51	-0.7 (0.8)	53	-0.7 (0.9)	47	-1.1 (0.7)
	5 to 10 Years	47	-1.2 (0.7)	42	-0.7 (0.9)	50	-0.8 (1)	40	-0.6 (0.7)	43	-0.7 (0.6)
	>10 Years	32	-1.1 (0.7)	26	-1.1 (0.7)	30	-0.4 (1.5)	34	-0.6 (0.7)	32	-0.7 (0.7)
Renal Function (eGFR)	60 to 90	77	-1.1 (0.7)	77	-0.9 (0.9)	79	-0.5 (1.2)	79	-0.5 (0.7)	72	-0.7 (0.6)
	≥90	60	-1.2 (0.8)	59	-1.2 (0.8)	62	-0.8 (0.9)	61	-0.8 (0.9)	60	-0.7 (0.9)
Hypertension	Yes	92	-1.1 (0.7)	95	-0.9 (0.9)	98	-0.6 (1)	95	-0.6 (0.8)	79	-0.6 (0.6)
	No	45	-1.2 (0.8)	41	-1.4 (0.7)	43	-0.6 (1)	45	-0.8 (0.7)	53	-0.8 (0.9)

Table 27: Other Subgroup Stats for Change in HbA1c in Treatment Naive Subjects

		Empa25/Lina5		Empa10/Lina5		Empa 25		Empa 10		Lina 5	
		N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)
Baseline HbA1c	<8.5	85	-0.6 (0.7)	84	-0.9 (0.8)	88	-0.7 (0.7)	82	-0.6 (0.6)	90	-0.5 (0.8)
	≥8.5	41	-1.9 (0.9)	36	-1.9 (0.9)	31	-1.5 (1.2)	31	-1.3 (1.2)	30	-1 (1.2)
BMI	<25	13	-1.3 (1)	15	-1.5 (1)	14	-1 (1.1)	13	-1.3 (0.9)	11	-0.2 (1)
	≥25	113	-1 (1)	105	-1.2 (1)	105	-0.9 (0.9)	100	-0.7 (0.9)	109	-0.7 (0.9)
Baseline Weight	≤70	18	-1.2 (1.1)	22	-1.7 (0.8)	22	-0.9 (0.8)	29	1.1 (0.9)	24	-0.4 (0.9)
	70 to 80	25	-0.9 (0.8)	24	-0.8 (1)	29	-1 (1.2)	21	-0.7 (0.8)	16	-0.6 (0.8)
	80 to 90	29	-1 (1.1)	25	-1.3 (1)	25	-0.7 (0.8)	16	-0.8 (1.1)	27	-0.9 (1)
	>90	54	-1.1 (0.9)	49	-1.1 (0.9)	43	-1 (0.9)	47	-0.6 (0.8)	53	-0.7 (1)
Ethnicity	Hispanic/Latino	44	-0.9 (1)	42	-1.3 (1)	38	-1 (1.1)	38	-1 (1)	35	-0.5 (0.9)
	Not H/L	82	-1.1 (1)	78	-1.2 (1)	81	-0.9 (0.8)	75	-0.7 (0.8)	85	-0.7 (1)
Time since T2DM	≤1 Year	38	-1.2 (1.1)	41	-1 (0.9)	40	-1.2 (0.9)	37	-0.9 (0.7)	44	-0.8 (1.1)
	1 to 5 Years	53	-0.8 (0.9)	40	-1.2 (0.8)	45	-0.8 (0.9)	49	-0.7 (1)	51	-0.5 (0.8)
	5 to 10 Years	25	-1 (0.9)	29	-1.5 (0.9)	21	-0.9 (1.1)	14	-0.9 (0.8)	21	-0.6 (1)
	>10 Years	10	-1.3 (0.8)	10	-1.1 (1.5)	13	-0.5 (0.7)	13	-0.5 (1.1)	4	-0.8 (0.8)
Renal Function (eGFR)	60 to 90	74	-0.9 (0.8)	70	-1.2 (1)	67	-0.7 (0.7)	65	-0.7 (0.8)	74	-0.9 (0.8)
	≥90	52	-1.1 (1.1)	50	-1.2 (1)	52	-1.2 (1.1)	48	-0.9 (1)	46	-0.5 (1)
Hypertension	Yes	64	-0.8 (0.9)	71	-1.1 (1)	71	-0.9 (0.9)	65	-0.9 (0.9)	79	-0.8 (0.9)
	No	62	-1.2 (1)	49	-1.3 (1)	48	-0.9 (1)	48	-0.7 (0.9)	41	-0.4 (1)
Baseline	≤4	23	-0.9 (0.9)	30	-1 (1.1)	36	-0.9 (1)	25	-0.9 (1)	35	-0.7 (1)

HOMA-IR	4 to 5.5	27	-1.1 (1.1)	28	-1.1 (0.8)	19	-0.6 (0.8)	22	-0.8 (0.8)	12	-0.8 (0.8)
	5.5 to 8.5	38	-1.1 (1)	28	-1.2 (0.9)	33	-1.1 (0.9)	23	-0.8 (0.9)	34	-0.6 (0.9)
	>8.5	38	-0.9 (1)	34	-1.4 (1)	31	-0.9 (1)	43	-0.7 (0.9)	39	-0.6 (1)
Baseline HOMA-IR	≤25	7	-1.6 (0.8)	12	-1 (1.5)	8	-0.8 (0.9)	5	-0.7 (1.4)	8	-0.7 (1)
	25 to 40	19	-1.4 (1)	13	-1.2 (1.1)	19	-1.1 (1)	18	-1 (1)	20	-0.5 (1.4)
	40 to 70	39	-1 (1.1)	34	-1.5 (0.9)	33	-0.9 (0.9)	36	-0.8 (0.9)	32	-0.7 (0.7)
	>70	61	-0.9 (0.8)	61	-1.1 (0.9)	59	-0.9 (0.9)	54	-0.7 (0.8)	60	-0.7 (0.9)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

- The biggest statistical issue for this study has to do with the failure of the primary and all secondary endpoints in achieving statistical significance as was pre-specified for the treatment naïve population. While there did appear to be some evidence of improved efficacy in this population, these results must be considered “exploratory”.
- A separate issue with this submission has to do with the lack of evidence of improved efficacy in both populations when comparing high FDC to low FDC. This was neither specified in the protocol nor provided in the submission. Post-hoc analyses to test the null hypothesis that the two FDCs were equivalent failed to be rejected showing no evidence of improved efficacy in terms of the chosen endpoints for the high FDC.
- Trial results for each population were not supportive of each other as analysis results were not significant for one population.

5.2 Collective Evidence

The addition of linagliptin to the FDC with high empagliflozin may not have any consequence in the effectiveness for the treatment naïve population as we see no statistical difference between high FDC and high dose empagliflozin monotherapy. Results from this study indicate a strong possibility for an efficacy ceiling. Moreover, the high FDC also did not indicate any improvements over low FDC in both populations. There were, however, significant results for the primary and several secondary endpoints in the metformin treated population. (b) (4) all positive results for the treatment naïve subjects can only be considered “exploratory” in nature, (b) (4)

Within the treatment naïve subjects in this study, there is some indication of improved efficacy for the low FDC. The testing hierarchy specified by the sponsor prevents them from using these results as anything but exploratory, so under regulatory procedure more evidence may be requested to approve the low FDC in this population. The results for low FDC on the primary endpoint were consistent against both monotherapy counterparts. However, formal testing was

not done for low FDC in the treatment naïve population for HbA1c as high FDC failed to achieve statistical significance against its monotherapy components in HbA1c change. It should be noted that in addition to the high FDC not showing improvement against its empagliflozin monotherapy counterpart in the primary and most of the secondary endpoints, the low FDC did not show improvement in FPG (p=0.06) and body weight (p=0.49) endpoints when compared to empagliflozin 10mg monotherapy. The effectiveness of the FDC remains uncertain in the treatment naïve population. An additional study may be necessary to reliably understand the effectiveness of the FDC in this population.

One possible reason for the differences in significance seen between the two populations is that of self-selection. Those in the metformin treated population may have switched therapies due to a lack of efficacy results in their current treatment. This would mean they could be a less healthy population when compared with the treatment naïve population. If there were a self-selection bias, then the treatment naïve subjects may have been able to tolerate and do well on any of the treatments.

5.3 Conclusions and Recommendations

Based on results found in this review, there is evidence for superiority of FDC when compared with monotherapy in the metformin treated population. There may also be some benefits over monotherapy in the treatment naïve population.

While there is some improvement seen in HbA1c by adding linagliptin to the low dose empagliflozin, the efficacy results do not hold when comparing high FDC to the high dose empagliflozin monotherapy in the treatment naïve population. There is also a lack of evidence showing improvement on the higher FDC when compared to the lower FDC in either population.

Based on these findings, there does not seem to be a requisite need for high FDC if low FDC is available. However, due to the fact that both high and low dose empagliflozin monotherapy will be available, the applicant cited benefit of ease of use, having only one pill instead of two, would be an improvement for patients who choose to take this higher FDC regimen.

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/s/

JENNIFER J CLARK
10/15/2014

RUTHANNA C DAVI
10/15/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 2060703

Applicant: Boehringer Ingelheim

Stamp Date: 1/30/2014

Drug Name: Empagliflozin and Lingliptin Tablets

NDA/BLA Type: Standard

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.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			There was only 1 study done for this combination product in two different populations. All efficacy and safety results are in the study report
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Key categories for subgroup analyses were age, baseline NbA1c, geographic region, sex, and renal impairment
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

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.	X			Even though only 1 key study is listed here it flows like 2 studies as there is a treatment naïve patient population and a metformin background population each with a separate defined

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

				hierarchical testing procedure.
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			No interim analyses were specified, investigators and patients were to remain blinded to treatment until database lock.
Appropriate references for novel statistical methodology (if present) are included.	X			No novel statistical methodology was used. Protocol specified methods included ANCOVA (with LOCF) and MMRM. There did, however, seem to be a slight difference in the ANCOVA model used in the study report from what was specified in the protocol.
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			

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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/s/

JENNIFER J CLARK
03/26/2014

MARK D ROTHMANN
03/28/2014
I concur