CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209091Orig1s000

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209091
Drug Name:	Saxagliptin/Dapagliflozin Fixed-Dose Combination (5 mg/10 mg)
Indication(s):	Type 2 diabetes mellitus
Applicant:	AstraZeneca Pharmaceuticals
Date(s):	Stamp: 4/27/2016 Due date 23/01/2016
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Anna Kettermann, Dipl. Math, MA
Concurring Reviewers:	Mark Rothmann, PhD, Team leader
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino, Pharm. D, Medical reviewer William Chong, MD, Clinical team leader
Project Manager:	Abolade Adeolu

Keywords: Missing data, subgroup analyses, regional differences, sensitivity analyses

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

AstraZeneca submitted a new NDA for a fixed dose combination (FDC) tablet of saxagliptin (5 mg) and dapagliflozin (10 mg). Both saxagliptin (saxa) and dapagliflozin (dapa) were previously approved as antihyperglycemic agents. Saxa-dapa was developed under IND 118840.

The goal of this submission was to examine effects of adding saxagliptin (saxa) to treatment of subjects with Type 2 diabetes (T2DM) who require additional glycemic control and currently on maximum recommended dose of dapagliflozin (10 mg) and metformin. The proposed FDC is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4)

The submission is comprised of three Phase 3 trials (CV181168 CV181169, and MB102129). Two of the studies (CV181169 and MB102129) were add-on studies (saxa was added to dapa in study CV181168, and dapa was added to saxa in study MB102129). The third study, trial CV181169, introduced both saxa and dapa concomitantly. All studies had a 24-week short-term efficacy period. Two add-on studies had an additional 28-week extension. Efficacy was evaluated only for the first 24-week period.
Because saxa-dapa FDC is only indicated to subjects who are already on maximum dose of dapa, the sponsor is seeking labeling only for the trial CV181168.

My recommendations:

Update the text of section 14 of the label (b) (4)
Instead, I would suggest providing the intent-to-treat (de facto) estimands, which consider the actual measurements of subjects regardless of adherence to treatment or use of subsequent therapy. A pattern-mixture imputation approach could be used to obtain those estimands.

I recommend including information on dropout rates by treatment group on the product label. Also, I suggest including information on rates of retrieved dropouts.

(b) (4)

(b) (4) I recommend that the paragraph titled be renamed "Proportion of patients known to have achieved HbA1c<7%" in order to make it clear that there were no formal testing of this hypothesis, i.e. there was no Type I error adjustment in calculation of these results.

Statistical Issues and findings

1. **Substantial evidence of efficacy.** In all Phase 3 studies, treatment with the saxa-dapa combination resulted in larger HbA1c reduction at week 24 than saxa or dapa alone when given in combination with metformin. Primary analysis results were consistent between sponsor's analyses and FDA analyses. Based on the FDA analysis examining data

obtained within the first 24 weeks from randomization, the HbA1c reduction in the saxa-dapa arm was larger than in the dapa arm without addition of saxa (0.3%, CI (0.2, 0.5) in study CV181168 and 0.3% CI(0.1, 0.5) in study CV181169). Similarly, saxa-dapa presented a larger reduction in HbA1c when it was compared to saxa without addition of dapa (0.5%, CI (0.3, 0.7) in study CV181169 and 0.6%, CI (0.4, 0.8) in study MB102129).

2. **Handling dropouts.** The sponsor's analysis did not take into account data of subjects who were rescued or dropped out prior to the end of the short-term efficacy period, thus evaluating only subjects who were able to tolerate the drug.

3. **Missing data.** The amount of missing data ranged between 5 and 10% across all studies. Study CV181169 had the largest amount of missing data, with the largest fraction of subject dropout in the dapa arm (12.3%). The lowest amount of missing data was observed among subjects in study CV181168, with the dapa arm having the lowest loss of subjects (3.7%). The largest fraction of subjects who discontinued the drug but had an HbA1c measurement at endpoint was observed in study MB102129 (7.5%, most of those subjects were from the saxa arm).

4. **Hierarchical testing for secondary endpoints.** In studies where dapa was compared to saxa-dapa (studies CV181169 and CV181168), the results of change in PPG (the first endpoint that was pre-specified in the hierarchy) were not significant. Therefore the testing for the secondary endpoints was stopped after the first comparison in those studies. In contrast, both, PPG and FPG comparisons yielded favorable results for saxa-dapa when the combination was compared to saxa without dapa.

5. **Subgroup analyses.** The effects of saxa-dapa were similar across all subgroups. Only when data were examined by region, a comparison between the saxa-dapa and dapa arms showed that the effect went in the opposite direction, favoring dapa, in North America. (The reduction in the dapa arm was larger than in the saxa-dapa arm in study CV181169 0.03% CI (-0.26, 0.32), while in study CV181168, the outcomes for the saxa-dapa arm showed lower efficacy in North America than in any other region when compared to dapa).

6. **Longitudinal changes in FPG.** Of note, the longitudinal changes in FPG had different patterns than changes in HbA1c, showing less difference in outcomes when treatment with saxa-dapa and dapa without saxa component were compared (studies CV181168 and CV181169). This leads me to conclude that the effect of saxa-dapa on all glucose parameters is not uniform. This outcome could be a result of larger variability of FPG as a biomarker.

2 INTRODUCTION

2.1 Overview

A brief description of the drug indication and history of the submission is presented below.

2.1.1 Indication

The goal of this submission was to examine effects of adding saxagliptin (saxa) to treatment of subjects with Type 2 diabetes (T2DM) who require additional glycemic control and currently on maximum recommended dose of dapagliflozin (10 mg) and metformin. The proposed FDC is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [redacted] (b) (4)

Saxagliptin is a dipetptidyl peptidase-4 (DPP4) inhibitor approved in 2009, available in 2.5 mg and 5 mg tablets. Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor approved in 2014, available in 5 mg and 10 mg tablets. While dapagliflozin is approved for monotherapy, it is typically prescribed as a second-line treatment in combination with metformin and/or other antihyperglycemic agents. Both drugs are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

2.1.2 History of Drug Developement

[redacted] (b) (4) the sponsor submitted an NDA [redacted] (b) (4) for the saxagliptin/dapagliflozin FDC tablets [redacted] (b) (4) Both saxagliptin (saxa) and dapagliflozin (dapa) were previously approved as antihyperglycemic agents. Saxa-dapa was developed under IND 118840. The NDA was based on the efficacy and safety results of study CV181169 where saxagliptin and dapagliflozin were added concomitantly (dual add-on) in T2DM patients who had inadequate glycemic control on metformin alone. The application received a Complete Response Letter (CRL) on 15 October 2015, in which FDA requested submission of additional clinical data [redacted] (b) (4)

Following type A meeting with the Agency, Astra Zeneca submitted a new NDA 209091 on 4/27/2016 for a fixed dose combination (FDC) tablet of saxagliptin (5 mg) and dapagliflozin (10 mg).

2.1.3 Specific Studies reviewed

The submission is comprised of three Phase 3 trials. Two of the studies (CV181169 and MB102129) were add-on studies (saxa was added to dapa in study CV181168, and dapa was added to saxa in study MB102129). The third study, trial CV181169, introduced both saxa and

dapa concomitantly. All studies had a 24-week short-term efficacy period. Two add-on studies had an additional 28-week extension. Efficacy was evaluated only for the first 24-week period. Because saxa-dapa FDC is only indicated to subjects who are already on maximum dose of dapa (10 mg), the sponsor is seeking labeling only for the trial CV181168.

Table 1. List of all Phase 3 studies included in analysis

	Phase and Design	Treatment Period	# of Subjects per Arm	Completed 24 weeks (%)
CV181168*	Randomized, double-blind, placebo-controlled, parallel group, sequential add-on	ST: 24 weeks (efficacy) LT: 28 weeks (extension)	Saxa+dapa 153 Pla+dapa 162	**Saxa+dapa 7.2** **Pla+dapa 3.7**
CV181169	Randomized, double-blind, active-controlled, parallel group, concomitant add-on	ST: 24 weeks (efficacy)	Saxa+dapa 179 Saxa 176 Dapa 179	**Saxa+dapa 5.5** **Saxa 8.5** **Dapa 10.6**
MB102129	**Randomized, double-blind, placebo-controlled, parallel group, sequential add-on**	**ST: 24 weeks (efficacy)** **LT: 28 weeks (extension)**	**Saxa+dapa 160** **Pla+saxa 160**	**Saxa+dapa 7.5** **Pla+saxa 4.4**

* Study included in the proposed label

2.2 Data Sources

This submission is in electronic common technical document (eCTD) format. The submission is archived at the following link: \\CDSESUB1\evsprod\NDA209091\209091.enx

Study datasets were provided as SAS XPORT transport files. The analysis datasets were joinable by unique identifier (SUBJID). The datasets were in good organization. Define.pdf file was clear

enough. My analysis on the primary and secondary efficacy endpoints gives approximately the same results as those reported in the clinical study report (CSR).

I derived from the submitted datasets all of the results presented in this review. I created all tables and figures in this review unless otherwise noted.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

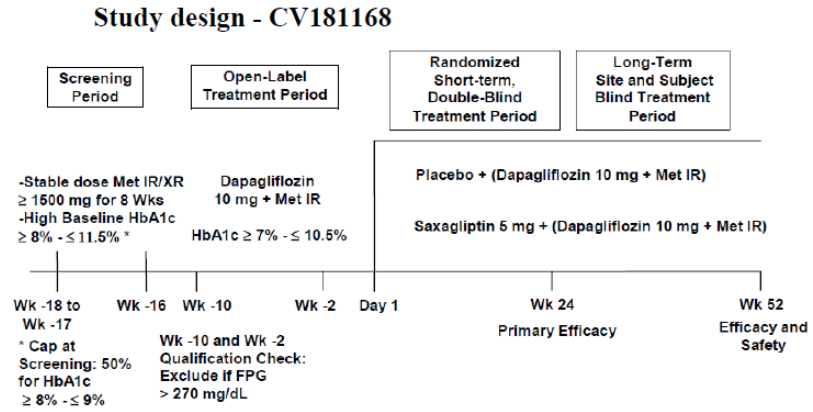
The submission quality was found to be reasonable.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

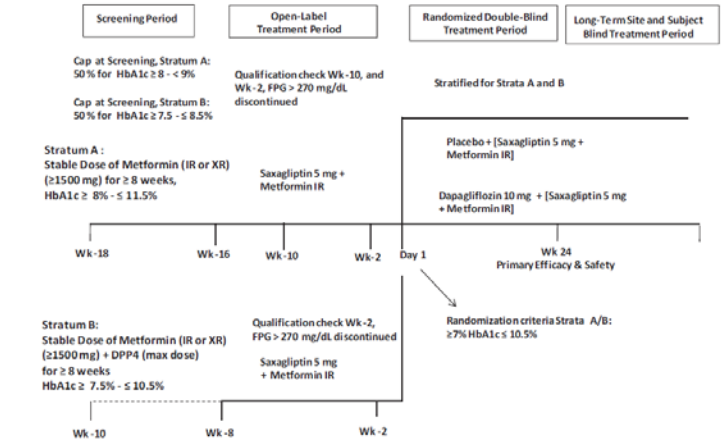
The submission consisted of three randomized, double-blind, placebo-controlled studies with parallel-group design. All three studies had a 24-week short-term efficacy period. Two add-on studies had an additional 28-week extension. Efficacy was evaluated only for the first 24-week period.
A schematic description of all three studies is presented below.

Figure 1. Design of study CV181168



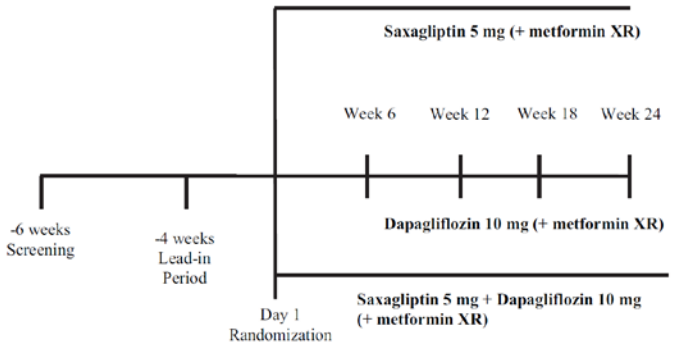
Source: Clinical overview p.26

Figure 2. Design of Study MB102129



Source: Clinical Study Report p. 3

Figure 3. Design of study CV181169



Source: Clinical Study report p. 3

All participants in all three studies were required to be on a stable dose of metformin prior to randomization. During lead-in period all subjects received open-label metformin. In Studies CV181168 and MB102129, saxagliptin and/or dapagliflozin were coadministered with metformin immediate release (IR). In Study CV181169, saxagliptin and/or dapagliflozin were coadministered with metformin extended release (XR). Both, metformin IR and XR were dosed at the upper end of the dose-response for metformin.

During all trials, study treatment and metformin were not to be titrated during the double-blind treatment period. The study drug was administered orally once daily.

Primary efficacy endpoint:
Change in HbA1c from baseline to week 24

Secondary efficacy endpoints:

1. Change in 2-hour post-prandial glucose (PPG) during a liquid meal test from baseline to week 24
2. Mean change from baseline to each time point in HbA1c and in fasting plasma glucose (FPG).
3. Percent of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, and time to glycemic rescue, or discontinuation, due to lack of efficacy, from baseline to each time point.

Control of type-I error:
The study-wise type-I error was controlled at 5% using a hierarchical testing strategy. Both two-sided p-values from the comparison of the monotherapies to Saxa-Dapa needed to be less than 0.05 to move to the subsequent level in the testing hierarchy.

Sample size calculations:
In all three studies, the sponsor's calculations of sample size were based on testing of the primary study endpoint, which was the change from baseline in HbA1c at the end of the 24-week, short-term double-blind, treatment period. All sample size calculations were made with the goal of detecting a difference in mean HbA1c change of 0.4% between Saxa-Dapa and each of the monotherapies assuming 90% power and a standard deviation of at least of 1.0%. The study-specific sample sizes are presented in the Table 2 located below.

Table 2. Sample size calculations

Study	CV181168	CV181169	MB102129
Total number of subjects	240	516	280
Number of subjects per arm	140	172	140
Power		90%	
Difference in HbA1c change		0.4%	
Standard deviation		1.0%	

3.2.2 Statistical Methodologies

Sponsor's approach:
Data analysis: A longitudinal repeated measures analysis was used to estimate the change in HbA1c and FPG from baseline; the model included the categorical fixed effects of treatment, week, and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Rescue was added as an additional categorical fixed effect in this mixed model when the analysis was performed on data regardless of rescue.

Primary analysis population and analysis dataset: The primary analysis population consisted of all randomized subjects that received at least one dose of study medication during the double-blind treatment period. HbA1c data obtained after discontinuation of protocol treatment were excluded from the primary analysis.

FDA approach:
Primary analysis and population: Because all post-discontinuation data points were excluded from the analysis, the sponsor's analysis examines the effect of week 24 HbA1c change under the assumption that no subject experienced rescue during the trial. I do not believe that in clinical practice none of the subjects for whom the drug is intended will need rescue. Thus, the outcomes based on this assumption might not be realistic. Also, subjects who discontinued treatment would not have the same outcomes as subjects who completed the entire treatment period. Analysis that excludes all post-discontinuation data will not represent all subjects who participated in the study. Therefore my analysis will include data regardless of adherence, i.e. all available data points collected after rescue or discontinuation will be included in the analysis. In my view, this approach more appropriately describes real world outcomes.

Also, in my analysis, I implemented a multiple imputation approach that imputed data for subjects who did not have HbA1c endpoint at week 24.

Imputation approach (retrieved dropouts ANCOVA):

1. First, 500 copies of the dataset were generated.
2. The imputation for subjects who did not have endpoint observation was performed using data from subjects who discontinued, but had post-rescue data (retrieved dropouts). Imputations were stratified by treatment group and baseline HbA1c.
3. For each dataset separately, the change in HbA1c at week 24 was analyzed using ANCOVA model. Each ANCOVA model contained baseline HbA1c and treatment group as covariates.
4. Results from an ANCOVA model fit to the imputed datasets were analyzed and combined using Rubin's method. Treatment effect estimates and limits from the 95% confidence interval (CI) were retained.

Sensitivity analyses:
Alternative imputation approach: Jump to Reference (J2R)
A pattern mixture model was used mimicking an ITT scenario where subjects who withdrew from the saxa-dapa group were assumed to be switched to the comparator treatment after withdrawal, while subjects treated with the comparator were assumed to remain on their assigned treatment throughout the trial. Subjects who withdrew from the saxa-dapa group were assumed to be switched to the comparator used in the trial.

Alternative imputation approach: Copy Reference (CR)
Similar to Jump to Reference approach, a pattern mixture model was used. The only difference to Jump to Reference is that subjects who withdrew from the saxa-dapa group were assumed to respond as if they had been treated with the comparator for the entire trial, while subjects treated with the comparator were assumed to remain on their assigned treatment throughout the trial.

Tipping point analysis
To further evaluate the robustness of the conclusions, a tipping point analysis of the approach assumed "copy reference" was performed. As described in the "copy reference" methodology above, in this analysis, subjects who withdrew from the saxa-dapa arm were assumed to have received a treatment inferior to the comparator. A 'penalty' was added to the endpoint HbA1c values that were imputed for the subjects who dropped out. The extent of 'penalty' was gradually increased to evaluate at which point saxa-dapa was no longer statistically significantly better than a comparator. This penalty value, also known as the tipping point, corresponded to a hypothetical degree of efficacy deterioration in withdrawn subjects needed to shift the treatment effect of saxa-dapa from being statistically significantly better than the comparator to a non-statistically significant effect.

MMRM analysis
Similar to the sponsor, a longitudinal repeated measures analysis was used to estimate the change in HbA1c from baseline until week 24; the model included the categorical fixed effects of treatment, week, and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. All analyses were performed using all data points obtained prior to and after the rescue/discontinuation.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Demographics and baseline characteristics are presented in Table 3 and in
Table 4. Overall, demographic characteristics were similar (Table 3). Most of the subjects were from North America (with exception of study mb102129). Subjects from study CV18168 had slightly lower baseline HbA1c then subjects in all other studies. Baseline values were consistent across arms within each study.

Table 3. Demographic table

		Trial	CV181168		CV181169		mb102129	
	Trial arm		Number of subjects	Percent	Number of subjects	Percent	Number of subjects	Percent
race	PLA + DAPA + MET	AMERICAN INDIAN/HAWAIIAN/ALASKA NATIVE	2	1.23	18	10.06		
		ASIAN	8	4.94	10	5.59		
		BLACK/AFRICAN AMERICAN	9	5.56	16	8.94		
		OTHER	2	1.23	4	2.23		
		WHITE	141	87.04	131	73.18		
	SAXA + DAPA + MET	AMERICAN INDIAN/ALASKA NATIVE			19	10.56		
		ASIAN	5	3.27	12	6.67	1	0.63
		BLACK/AFRICAN AMERICAN	11	7.19	22	12.22	8	5.00
		OTHER	1	0.65	7	3.89	1	0.63
		WHITE	136	88.89	120	66.67	150	93.75
	SAXA+ MET	AMERICAN INDIAN/HAWAIIAN/ALASKA NATIVE			18	10.23	2	1.26
		ASIAN			11	6.25	1	0.63
		BLACK/AFRICAN AMERICAN			22	12.50	10	6.25
		OTHER			4	2.27		
		WHITE			121	68.75	147	1.88
sex	PLA + DAPA + MET	Male	76	46.91	89	49.72		
		Female	86	53.09	90	50.28		
	SAXA + DAPA + MET	Male	73	47.71	85	47.22	70	43.75
		Female	80	52.29	95	52.78	90	56.25
	SAXA+ MET	Male			94	53.41	76	47.50
		Female			82	46.59	84	52.50
region	PLA + DAPA + MET	EUROPE	55	33.95	40	22.35		
		LATIN AMERICA	21	12.96	38	21.23		
		NORTH AMERICA	86	53.09	100	55.87		
		ASIA/PACIFIC			1	0.56		
	SAXA + DAPA + MET	EUROPE	55	35.95	40	22.22	51	31.88
		LATIN AMERICA	20	13.07	40	22.22	54	33.75
		NORTH AMERICA	78	50.98	98	54.44	55	34.38
		ASIA/PACIFIC			2	1.11		
	SAXA+ MET	EUROPE			34	19.32	63	39.38
		LATIN AMERICA			40	22.73	49	30.63
		NORTH AMERICA			99	56.25	48	30.00
		ASIA/PACIFIC			3	1.7		

Table 4. Baseline data (Age and HbA1c)

	Arm	N		N	Median	Minimum	Maximum	Mean	Std Dev	Coeff of Variation
Study cv181168	PLA + DAPA + MET	162	Age	162	55.0	27.0	78.0	54.5	9.3	17.1
			Baseline Value	160	7.7	5.2	10.1	7.8	0.9	11.7
			Change from Baseline	162	-1.7	-4.6	1.7	-1.6	1.2	-74.5
			Length of follow-up (weeks)*	162	24.0	0.0	24.0	23.4	3.1	13.3
	SAXA + DAPA + MET	153	Age	153	56.0	27.0	77.0	54.7	9.8	18.0
			Baseline Value	150	7.8	6.3	10.9	7.9	0.8	10.4
			Change from Baseline	152	-1.8	-4.8	0.9	-1.9	1.3	-66.7
			Length of follow-up (weeks)*	153	24.0	4.0	24.0	23.2	3.4	14.6
Study cv181169	DAPA + MET	179	Age	179	54.0	29.0	81.0	53.5	9.7	18.1
			Baseline Value	172	8.8	6.2	12.3	8.9	1.2	13.2
			Change from Baseline	172	-1.1	-5.0	1.2	-1.2	1.1	-95.2
			Length of follow-up (weeks)*	179	24.0	0.0	24.0	22.1	5.7	25.8
	SAXA + DAPA + MET	180	Age At Consent Date	180	55.0	30.0	78.0	53.4	9.8	18.4
			Baseline Value	176	8.7	6.2	12.1	8.9	1.2	13.3
			Change from Baseline	176	-1.6	-5.3	2.6	-1.5	1.2	-80.6
			Length of follow-up (weeks)*	180	24.0	0.0	24.0	22.8	4.6	20.3
	SAXA + MET	176	Age At Consent Date	176	55.0	24.0	74.0	54.6	9.6	17.7
			Baseline Value	175	8 9	6.8	12.3	9.0	1.1	11.7
			Change from Baseline	175	-0.9	-4.8	2.6	-1.0	1.1	-111.6
			Length of follow-up (weeks)*	176	24.0	0.0	24.0	22.8	4.2	18.3
Study mb102129	DAPA + SAXA + MET	160	Age At Consent Date	160	56.0	33.0	72.0	55.2	8.6	15.6
			Baseline Value	158	8 1	6.3	11.4	8.2	1.0	11.8
			Change from Baseline	160	-1.7	-5.5	2.0	-1.7	1.2	-67.5
			Length of follow-up (weeks)*	160	24.0	4.0	24.0	23.0	3.9	16.8
	PLA + SAXA + MET	160	Age At Consent Date	160	56.0	30.0	75.0	55.0	9.6	17.4
			Baseline Value	158	8.0	6.3	11.8	8.2	1.0	12.1
			Change from Baseline	160	-1.2	-4.1	2.5	-1.1	1.2	-107.1
			Length of follow-up (weeks)*	160	24.0	4.0	24.0	23.1	3.8	16.3

Missing data

Overall, the amount of missing data in all three trials was not very large (5-10%). Study CV181169 had the largest fraction of subjects who dropped out prior to their 24-week visit. In contrast, study CV181168 had the lowest dropout rate. The largest fraction of subjects who were put on rescue therapy and had HbA1c measurement at week 24 (retrieved dropouts) was observed in study MB102129 (7.5%). A graphical illustration of dropout and rescue patterns in each study is shown in the appendix (Figure 13).

Table 5. Missing data by study

Study		SAXA+DAPA	DAPA	SAXA	Total
CV181168	Missing	10* (6.5%)	6 (3.7%)		16 (5.1%)
	Retrieved	4 (2.6%)	7(4.3%)		11(3.5%)
CV181169	Missing	14(7.8%)	22 (12.3%)	17(9.7%)	53(9.9%)
	Retrieved	8(4.4%)	6(3.4%)	17(9.7%)	31(5.8%)
MB102129	Missing	12(7.5%)		11(6.9%)	23(7.2%)
	Retrieved	2(1.2%)		22(13.8%)	24(7.5%)

*Table 5.1-1p. 47 Clinical Study Report indicates that there were 11 subjects who dropped out, but the submitted dataset contained data on 143 (i.e. only 10 subjects were missing) subjects at week 24. The discrepancy could be due to the fact that sponsor excluded post-rescue data from the analysis.

During my review I identified one study (CV181168) where an entire region (Latin America) did not have any dropouts or rescue during the 24-week efficacy period. All subjects from Latin America came from four study sites located in Mexico (study sites 0072, 0073, 0074, and 0075).

The results presented in Table 6 are illustrating missing data patterns by treatment group and region. No robust conclusion on all those patterns could be made because the number of dropouts was small. Of note, the number of subjects who dropped out of the study was larger among study participants from North America. This pattern could be partially explained by the fact that the largest number of subjects came from North America, although study CV181169 had disproportionally many dropouts among subjects from North America. Overall, study CV181169 had the largest amount of missing data.

Table 6. Missing data by study and treatment group

Study	ARMCD	REGION	Retrieved*	Dropout**
CV181168	PLA + DAPA	EUROPE	1	2
		NORTH AMERICA	6	4
	SAXA + DAPA	EUROPE		2
		NORTH AMERICA	4	8
CV181169	DAPA	EUROPE		2
		LATIN AMERICA	3	4
		NORTH AMERICA	3	16
	SAXA + DAPA	EUROPE		1
		LATIN AMERICA	4	2
		NORTH AMERICA	4	11
	SAXA	EUROPE	1	2
		LATIN AMERICA	7	3
		NORTH AMERICA	9	12
MB102129	DAPA + SAXA	EUROPE	2	2
		LATIN AMERICA		5
		NORTH AMERICA		5
	PLA + SAXA	EUROPE	11	3
		LATIN AMERICA	6	3
		NORTH AMERICA	5	5

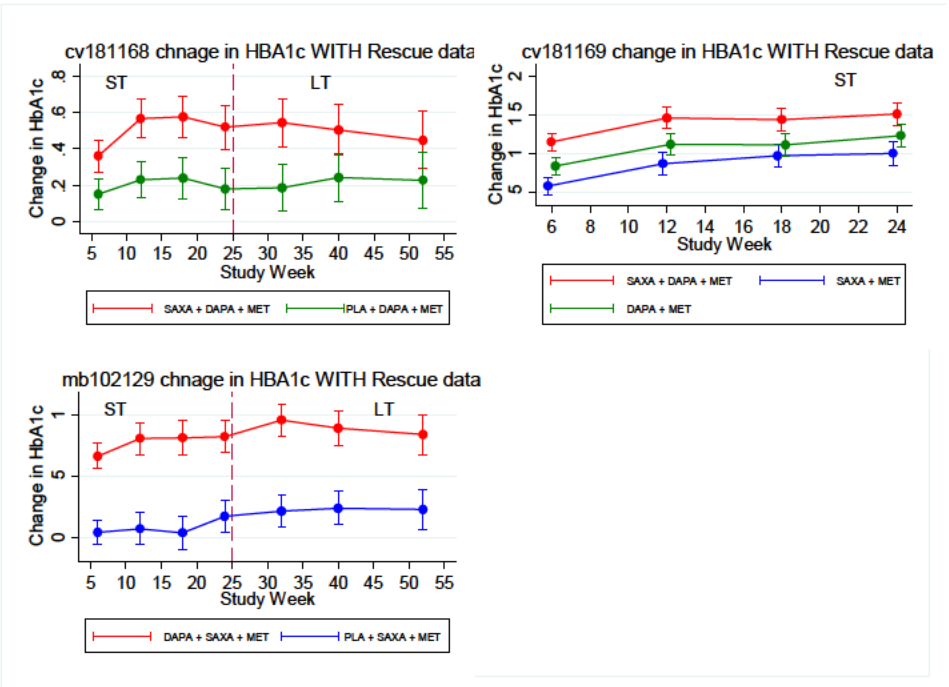
*Subjects who discontinued protocol treatment and had a 24-week evaluation
* Subjects who did not have an observation at week 24

3.2.4 Results and Conclusions

3.2.4.1 Graphical exploration

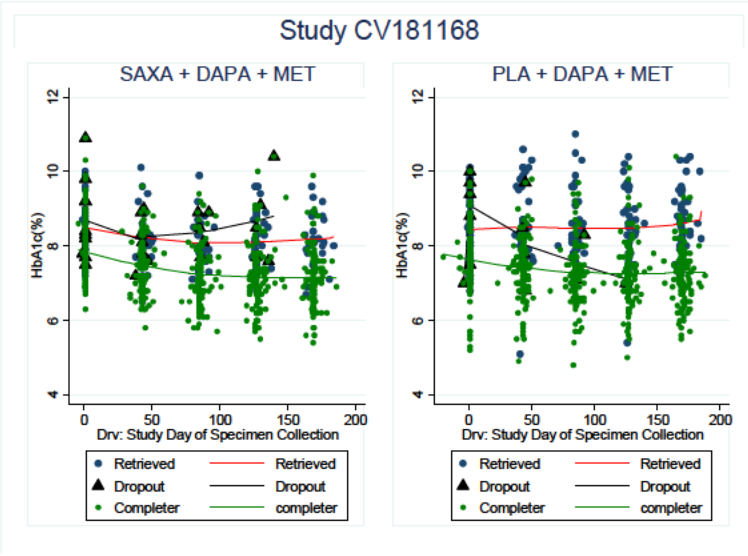
An illustration of longitudinal changes of HbA1c by study is presented in Figure 4. Of note, the difference between saxa-dapa and its components becomes smaller after the short-term efficacy period is over. The reason of such a change could possibly be because of the discontinuation pattern during the safety part of the study.

Figure 4. Longitudinal changes in HbA1c (MMRM analysis)



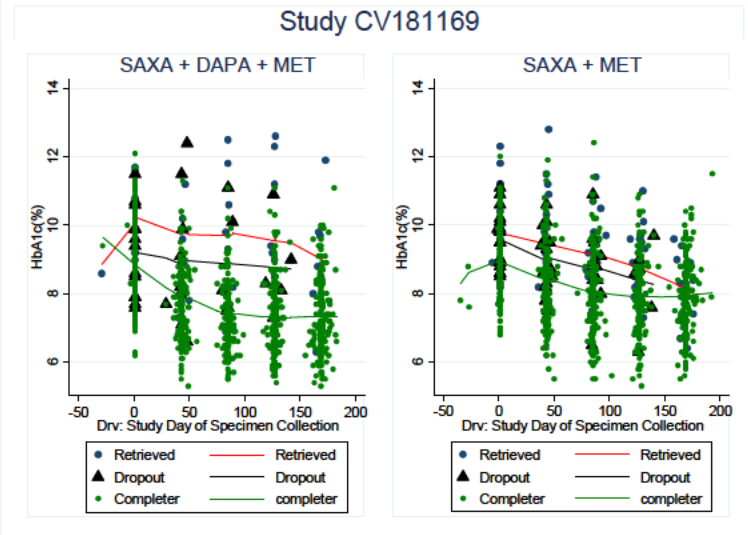
A simple graphical comparison of longitudinal HbA1c patterns based on study completion status (completers, dropouts, and subjects who were retrieved) is presented in Figure 5, Figure 6, and in Figure 7, suggesting that subjects who were retrieved had less reduction in HbA1c than subjects who stayed on protocol treatment. Also, in most of the cases, subjects who dropped out, i.e. did not have a 24-week evaluation, had HbA1c values aligned closer with values of retrieved subjects. An examination of these patterns suggests that multiple imputation approach based on retrieved dropout is a reasonable method for analysis of these data.

Figure 5. Study CV181168: Longitudinal changes based on completion status



Legend: Scatter plot of HbA1c versus study day. Each circle/triangle represents a different measurement of HbA1c, thus one subject is contributing to the plot multiple times. Values obtained from subjects who competed the 24-week study period are represented by green circles, the retrieved subjects are presented by blue circles and subjects who dropped out are presented by black triangles. Lowess curves were fitted for each group for the purpose of visual comparisons

Figure 6. Study CV181169: Longitudinal changes based on completion status



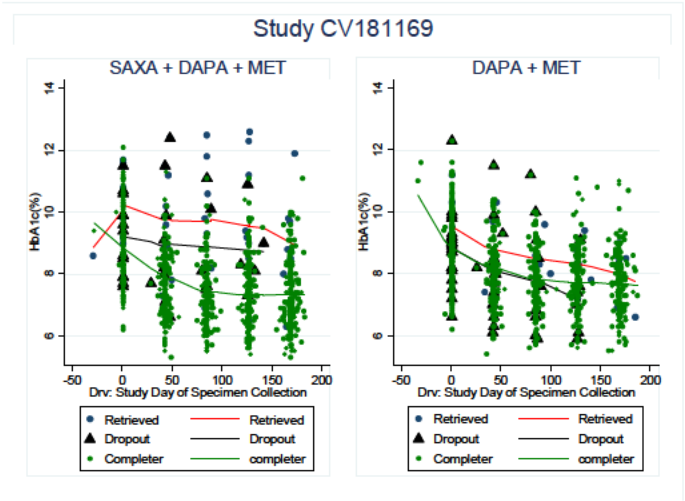
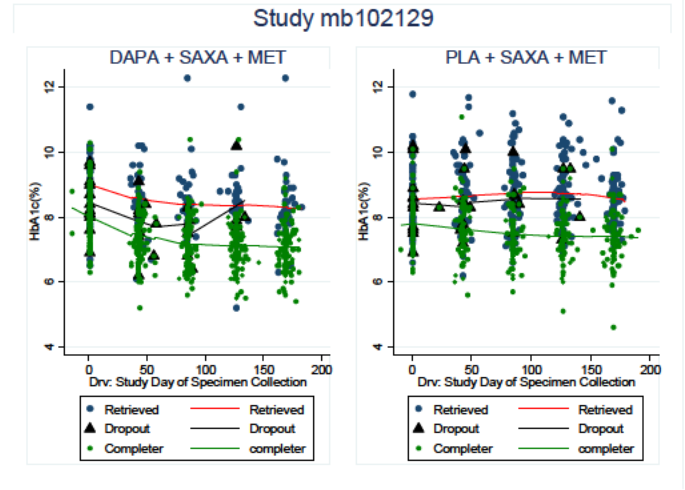


Figure 7. MB102129: Longitudinal changes based on completion status



3.2.4.2 Primary analysis

The results of pre-specified primary analysis (MMRM without data after rescue) conducted by the sponsor are presented in Table 7. In all three studies, subjects on the saxa-dapa combination showed a greater 24-week HbA1c reduction than subjects who were taking each of its components. Therefore, saxa-dapa met its goal based on pre-specified testing, and therefore demonstrated that the combination of saxa and dapa provides additional HbA1c reduction beyond reduction obtained by use of each of its components.

Table 7. Sponsor's results (24 weeks)*

Study	SAXA + DAPA vs	MMRM
CV181168	DAPA	-0.35 (-0.52, -0.18)
CV181169	DAPA	-0.27 (-0.48, -0.05)
	SAXA	-0.59 (-0.81, -0.37)
MB102129	SAXA	-0.72 (-0.91,-0.53)

*Excludes data after rescue or discontinuation

The results of my analysis are presented in the Table 8 below. The results for my MMRM (which included data after rescue) were very close to the results that were provided by the sponsor. The outcomes obtained from the analysis that utilized the most appropriate multiple imputation method (based on retrieved dropouts) were slightly more modest, but all of them demonstrated that combination of saxa and dapa provided a greater reduction of HbA1c than each of its components separately. Although the results obtained by the sponsor and my results were numerically similar, as I pointed out in section 3.2.2, both of these analyses are examining different questions, i.e. an estimand based on different assumptions.

The robustness of outcomes was examined using tipping point analysis. The results of tipping point analysis based on the retrieved dropout multiple imputation method show that it would take impractical circumstances to tip the results from being favorable for saxa-dapa to being favorable for one of its components.

Table 8. FDA results (24 weeks)**

Study	SAXA + DAPA vs	MI (J2R)	MI (CR)	MI (retrieved dropouts ANCOVA)	MMRM	Tipping point delta
CV181168	DAPA	-0.336 (-0.504, -0.166)	-0.334 (-0.505, -0.167)	-0.395 (-0.54, -0.233)	-0.337 (-0.504, -0.171)	2.2
CV181169	DAPA	-0.194 (-0.45, -0.062)	-0.281 (-0.489, 0.072)	-0.186 (-0.48, 0.108)	-0.283 (-0.495, -0.071)	0.8
	SAXA	-0.362 (-0.598, -0.127)	-0.489 (-0.706,-0.271)	-0.354 (-0.6, -0.107)	-0.517 (-0.728,-0.306)	2.8
MB102129	SAXA	-0.63 (-0.827, -0.436)	-0.6 (-0.778, -0.423)	-0.633 (-0.828, -0.438)	-0.65 (-0.832, -0.467)	4.2

**All analyses included data after rescue or discontinuation

3.2.4.3 Analysis of secondary endpoints

This section summarizes results from the applicant's analysis of key secondary endpoints.

FPG and PPG
All results presented by the sponsor are summarized in Table 9. From the sponsor's results, it is clear that all comparisons of FPG and PPG failed to show that saxa-dapa was more efficacious than dapa alone. As specified in the statistical analysis plan, the hierarchical significance testing for the other secondary endpoints was stopped at this endpoint and no further formal statistical testing was performed.

Table 9. Fasting plasma glucose and 2 hour post-prandial glucose*

Study		SAXA+DAPA vs	Difference	95% CI
CV181168	PPG	DAPA	-5.9	(-14.9, 3.1)
	FPG	DAPA	-3.7	(-11.0, 3.6)
CV181169	PPG	SAXA	-44	(-53.7, -34.3)
		DAPA	-9.1	(-18.8, 0.5)
	FPG	SAXA	-23.8	(-31.6, -15.9)
		DAPA	-6.1	(-13.8, 1.7)
MB102129	FPG	SAXA	-27.7	(-35.3, -20.1)

*post-rescue or -discontinuation data not included

A graphical illustration showing side by side comparison of HbA1c and FPG patterns is presented in Figure 8 and in Figure 9 below.

Figure 8. Longitudinal changes HbA1c and FPG Study CV181169

Figure 7.2-1: Longitudinal Plot of Change from Baseline in HbA1c - 24-Week Double Blind Period - Randomized Subjects

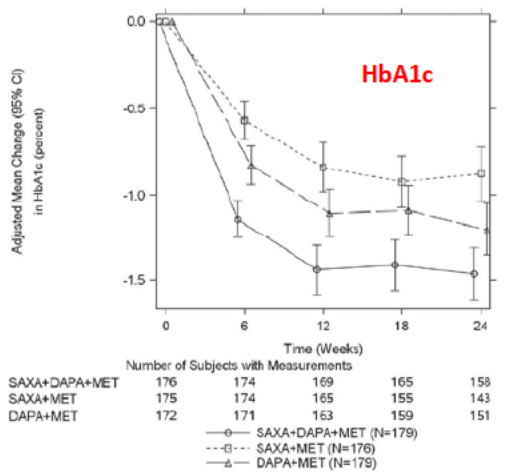


Figure 7.3.2-1: Longitudinal Plot of Change from Baseline in FPG - 24-Week Double-blind Treatment Period - Randomized Subjects

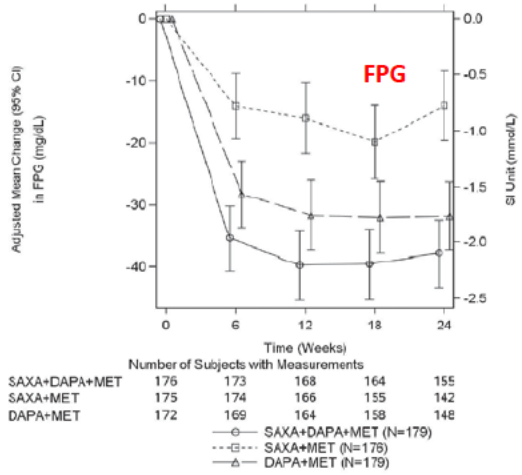


Figure 9. Longitudinal changes HbA1c and FPG Study CV181168

Figure 7.2.1-1: Longitudinal Plot of Adjusted Mean Change from Baseline in HbA1 52-Week Double-Blind Period, Excluding Data after Rescue, Randomized Subjects

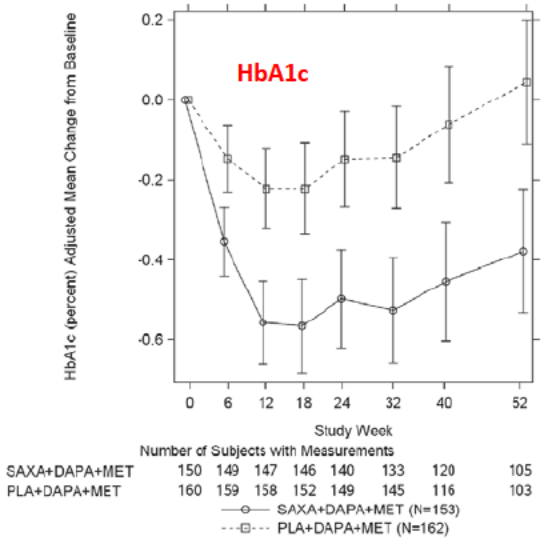
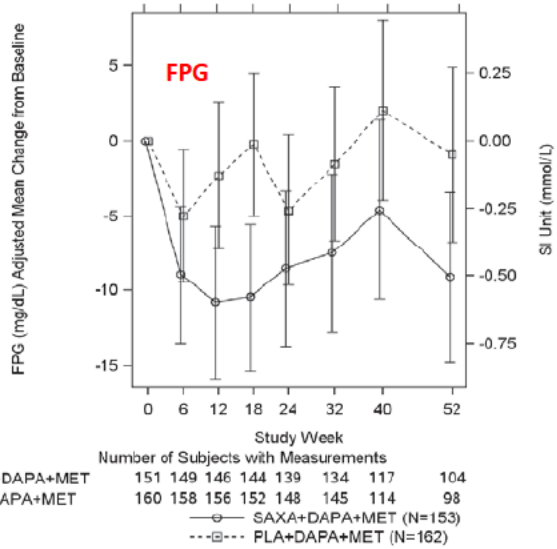


Figure 7.2.2-1: Longitudinal Plot of Adjusted Mean Change from Baseline in H Short-term + Long-term Treatment Period, Excluding Data Af Rescue, Randomized Subjects



HbA1c<7%

The differences in the proportion of patients achieving the benchmark for saxa-dapa are presented in the table below. Subjects discontinued or rescued prior to week 24 or missed measurements at week 24 were considered not achieving glycemic response.

Table 10. Subjects with HbA1c <7% at week 24

Study	SAXA+DAPA vs	Difference	95% CI
CV181168	DAPA	12	(3, 21)
CV181169	SAXA	19	(9,28)
	DAPA	15	(7, 24)
MB102129	SAXA	17	(8, 25)

3.3 Evaluation of Safety

Safety events were reviewed by Dr. Frank Pucino from Medical Division of Metabolism and Endocrinology Products. Readers are referred to Dr. Pucino's review for this section.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes results from the analysis of the primary efficacy endpoint within subgroup levels. The subgroups explored are

- Sex (females; males)
- Age (< 65 years; ≥ 65 years)
- Race (white; non-white)
- Region (Europe, Latin America, North America)
- Baseline HbA1c (<7.5%; ≥ 7.5% and <9.0%; ≥ 9.0%)

4.1 Sex, Race, Age, and Geographic Region

The subgroup analyses were performed using the same approach as primary analysis.

In all three studies, both, male and female participants had a larger HbA1c reduction on the saxa-dapa combination treatment than on saxa or dapa alone (Table 11).

Table 11. Subgroup analysis by sex

Study	Saxa-Dapa -	Estimate	CI		Subgroup
CV181168	DAPA	-0.346901	(-0.58391,	-0.10989)	MALE
	DAPA	-0.309387	(-0.55121,	-0.06756)	FEMALE
MB102129	SAXA	-0.808769	(-1.07085,	-0.54669)	MALE
	SAXA	-0.435266	(-0.69972,	-0.17081)	FEMALE
CV181169	SAXA	-0.499968	(-0.80120,	-0.19873)	MALE
	SAXA	-0.491517	(-0.81797,	-0.16506)	FEMALE
	DAPA	-0.395690	(-0.70397,	-0.08741)	MALE
	DAPA	-0.181993	(-0.46617,	0.10218)	FEMALE

The subgroup analysis by race did not show consistencies across studies when subjects other than white were examined. This could be due to the fact that the number of non-white subjects in the saxa-dapa program was small (Table 12).

Table 12. Subgroup analysis by race

Study	Saxa-Dapa -	Estimate	CI		Subgroup	N subjects*
CV181168	DAPA	0.463633	(-0.3544,	1.2817)	ASIAN	13
	DAPA	-0.485527	(-1.3402,	0.3692)	BLACK/AFRICAN AMERICAN	20
	DAPA	-0.338455	(-0.5132,	-0.1637)	WHITE	277
MB102129	SAXA	0.520768	(-0.7427,	1.7843)	BLACK/AFRICAN AMERICAN	18
	SAXA	-0.661277	(-0.8475,	-0.4750)	WHITE	297
CV181169	SAXA	-0.306890	(-1.1171,	0.5033)	AMERICAN INDIAN/ALASKA NATIVE	37
	SAXA	-0.464165	(-1.2838,	0.3555)	ASIAN	23
	SAXA	-0.847328	(-1.4309,	-0.2637)	BLACK/AFRICAN AMERICAN	44
	SAXA	-0.414399	(-0.6810,	-0.1478)	WHITE	241
	DAPA	-0.128608	(-0.9857,	0.7284)	AMERICAN INDIAN/ALASKA NATIVE	37
	DAPA	-0.368833	(-1.0020,	0.2643)	BLACK/AFRICAN AMERICAN	38
	DAPA	-0.290290	(-0.5378,	-0.0428)	WHITE	251

*Number of subjects in each separate calculation (Some of the race groups did not have sufficient number of subjects to draw meaningful conclusions; those comparisons are not included in this table. Because in study CV181169, saxa-dapa was compared to both, saxa and dapa, the number of subjects in this column will not be the same as the number of subjects in the study).

The subgroup analysis by age also showed that subjects in all age subgroups had a larger reduction of HbA1c on saxa-dapa than subjects on saxa or dapa alone. Of note, the efficacy of saxa-dapa was larger among younger people (<65) when saxa-dapa was compared to saxa alone (studies MB102129 and CV181169). The effect was lower among subjects of age 65 or older (Table 13).

Table 13. Subgroup analysis by age

Study	Saxa-Dapa -	Estimate	CI		Subgroup
CV181168	DAPA	-0.334258	(-0.52125,	-0.14727)	< 65
	DAPA	-0.304935	(-0.68721,	0.07734)	>= 65
MB102129	SAXA	-0.636545	(-0.83931,	-0.43378)	< 65
	SAXA	-0.429769	(-0.91050,	0.05096)	>= 65
CV181169	SAXA	-0.517148	(-0.76597,	-0.26833)	< 65
	SAXA	-0.298983	(-0.78948,	0.19152)	>= 65
	DAPA	-0.269872	(-0.49573,	-0.04402)	< 65
	DAPA	-0.384605	(-0.89913,	0.12992)	>= 65

In all three studies, subjects from North America showed a smaller HbA1c reduction among subjects treated with saxa-dapa (compared to saxa or dapa alone) than subjects on the same treatment who were from Europe or Latin America (Table 14). When saxa-dapa was compared to dapa in study CV181169, the results for North America were .028(-0.027, 0.324) in favor of dapa alone. When saxa-dapa was compared to dapa alone in study CV181168, the outcomes for all regions (including North America) showed a larger reduction among in saxa-dapa treatment than on dapa alone. In this study, the effect was smaller among subjects from North America, the confidence interval came close to but did not include zero.

Table 14. Subgroup analysis by region

Study	Saxa-Dapa -	Estimate	CI		REGION
CV181168	DAPA	-0.393997	(-0.6751,	-0.1129)	EUROPE
	DAPA	-0.557534	(-1.0178,	-0.09726)	LATIN AMERICA
	DAPA	-0.245554	(-0.4829,	-0.00825)	NORTH AMERICA
MB102129	SAXA	-0.573148	(-0.8799,	-0.26639)	EUROPE
	SAXA	-0.815899	(-1.14979,	-0.48201)	LATIN AMERICA
	SAXA	-0.482445	(-0.82107,	-0.14382)	NORTH AMERICA
CV181169	SAXA	-0.650007	(-1.0189,	-0.2812)	EUROPE
	SAXA	-0.910636	(-1.3088,	-0.5125)	LATIN AMERICA
	SAXA	-0.257646	(-0.5903,	0.075)	NORTH AMERICA
	DAPA	-0.669419	(-1.0123,	-0.3256)	EUROPE
	DAPA	-0.637687	(-1.0614,	-0.214)	LATIN AMERICA
	DAPA	0.027895	(-0.2682,	0.324)	NORTH AMERICA

4.2 Other Special/Subgroup Populations

Additional subgroup analyses were conducted based on baseline HbA1c cut points. A brief graphical exploration of HbA1c changes stratified by baseline HbA1c is presented in Figure 10, Figure 11, and Figure 12. In all studies, the line for saxa-dapa (dashed line in each of the graphs) demonstrated a larger reduction in HbA1c from baseline during the entire study period (in all comparisons the dashed line ends up being lower than all the comparators). The absolute reduction in HbA1c was larger among subjects who had higher baseline HbA1c values than among subjects who started with lower HbA1c values. In study mb102129, subjects on saxa alone who started in the lower baseline category had an increase in HbA1c towards the end of the study (Figure 11). These findings suggest that baseline level plays an important role in the interpretation of the outcomes, and, therefore, it is crucial to account for baseline HbA1c level in the analyses.

Figure 10. HbA1c stratified by baseline HbA1c Study cv181168

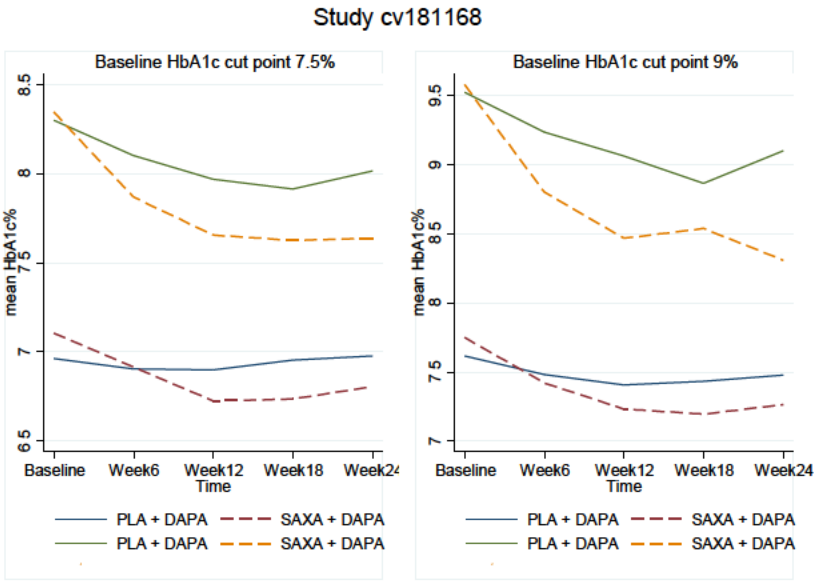


Figure 11. HbA1c stratified by baseline HbA1c Study mb102129

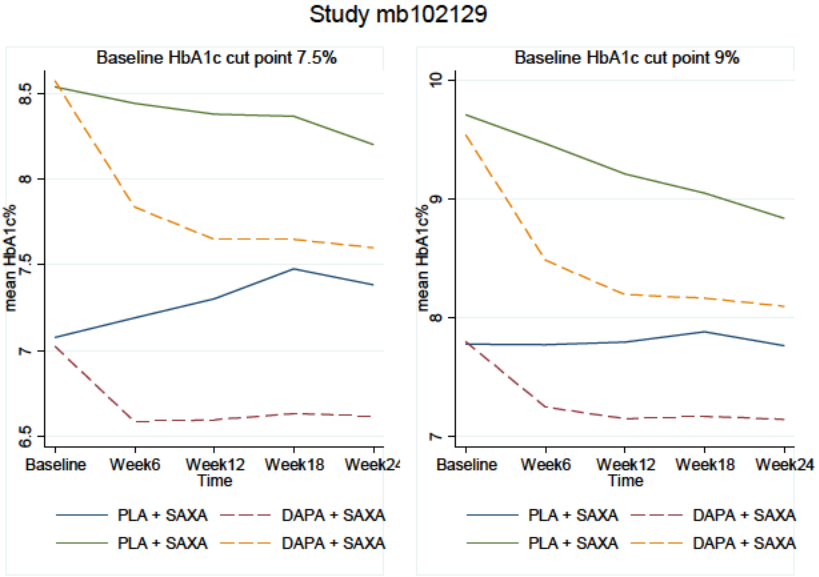
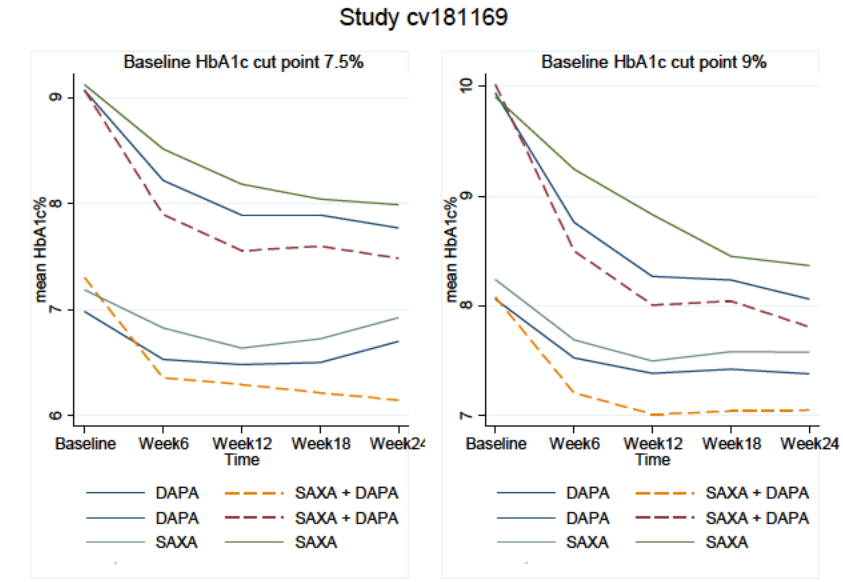


Figure 12. HbA1c stratified by baseline HbA1c Study cv181169



The results for subgroups classified by baseline HbA1c cut points (7.5% and 9%) are presented in Table 15).

Table 15. Subgroup analysis by baseliene HbA1c

Study	Saxa-Dapa -	Estimate	CI	Subgroup
CV181168	DAPA	-0.277030	(-0.50419, -0.04987)	<7.5
	DAPA	-0.361006	(-0.58641, -0.13560)	>=7.5
	DAPA	-0.293611	(-0.46757, -0.11965)	<9
	DAPA	-0.607226	(-1.20487, -0.00958)	>=9
MB102129	SAXA	-0.708373	(-1.08850, -0.32825)	<7.5
	SAXA	-0.564883	(-0.78141, -0.34836)	>=7.5
	SAXA	-0.597805	(-0.80338, -0.39222)	<9
	SAXA	-0.586266	(-1.03736, -0.13518)	>=9
CV181169	SAXA	-0.633913	(-1.4958, 0.2279)	<7.5
	SAXA	-0.458229	(-0.6906, -0 2258)	>=7.5
	SAXA	-0.351375	(-0.63495, -0.06780)	<9
	SAXA	-0.536076	(-0.88488, -0.18727)	>=9
	DAPA	-0.648547	(-1.19853, -0.09856)	<7.5
	DAPA	-0.259413	(-0.48088, -0.03794)	>=7.5
	DAPA	-0.312302	(-0.57277, -0.05184)	<9
	DAPA	-0.241836	(-0.57877, 0.09510)	>=9

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Resolved issues:

1. **Substantial evidence of efficacy.** In all Phase 3 studies, treatment with saxa-dapa combination resulted in larger HbA1c reduction at week 24 than saxa or dapa alone when given in combination with metformin. Primary analysis results were consistent between sponsor's analyses and FDA analyses. Based on FDA analysis examining data obtained within the first 24 weeks from randomization, the HbA1c reduction in saxa-dapa arm was larger than is in dapa arm without addition of saxa (0.3%, CI (0.2, 0.5) in study CV181168 and 0.3% CI(0.1, 0.5) in study CV181169). Similarly, saxa-dapa presented a larger reduction in HbA1c when it was compared to saxa without addition of dapa (0.5%, CI (0.3, 0.7) in study CV181169 and 0.6%, CI (0.4, 0.8) in study MB102129).

2. **Handling of dropouts.** The sponsor's analysis did not take data of subjects who were rescued or dropped out prior to the end of the short-term efficacy period into account, thus evaluating only subjects who were able to tolerate the drug.

3. **Missing data.** The amount of missing data ranged between 5 and 10% across all studies. Study CV181169 had the largest amount of missing data with the largest fraction of dropout subjects in the dapa arm. The lowest amount of missing data was among subjects in study CV181168 with the dapa arm having the lowest loss of subjects (3.7%). The largest fraction of subjects who discontinued the drug (retrieved dropout) was observed in study MB102129 (7.5%, most of those subjects were from saxa arm).

Issues not resolved or only partially resolved in this submission:

4. **Subgroup analyses.** The effects of saxa-dapa were similar across all subgroups. Only when data were examined by region, a comparison between the saxa-dapa and dapa arms showed that the effect went in the opposite direction, favoring dapa, in North America. (The reduction in the dapa arm was larger than in the dapa-saxa arm in study CV181169 0.03% CI (-0.26, 0.32), while in study CV181168, the outcomes for the dapa-saxa arm showed the lower efficacy in North America than in any other region when compared to dapa. The causes for those outcomes cannot be explained.

5.

   A) Hierarchical testing for secondary endpoints. In studies where dapa was compared to dapa-saxa (studies CV181169 and CV181168), the results of change in PPG (the first endpoint that was pre-specified in the hierarchy) were not significant. Therefore the testing for the secondary endpoints was stopped after the first comparison in those studies. In contrast, both, PPG and FPG comparisons yielded favorable results for dapa-saxa when the combination was compared to saxa without dapa.

B) Longitudinal changes in FPG. Of note, the longitudinal changes in FPG had different patterns than changes in HbA1c, showing less difference in outcomes when treatment with dapa-saxa and dapa without the saxa component were compared (studies CV181168 and CV181169). That leads me to conclude that the effect of saxa-dapa on all glucose parameters is not uniform. This outcome could be a result of larger variability of FPG as a biomarker.

5.2 Collective Evidence

Substantial evidence of efficacy. In all Phase 3 studies, treatment with the saxa-dapa combination resulted in larger HbA1c reduction at week 24 than saxa or dapa alone when given in combination with metformin. Primary analysis results were consistent between sponsor's analyses and FDA analyses. Based on FDA analysis examining data obtained within the first 24 weeks from randomization, the HbA1c reduction in the saxa-dapa arm was larger than in the dapa arm without addition of saxa (0.3%, CI (0.2, 0.5) in study CV181168 and 0.3% CI(0.1, 0.5) in study CV181169). Similarly, saxa-dapa presented a larger reduction in HbA1c when it was compared to saxa without addition of dapa (0.5%, CI (0.3, 0.7) in study CV181169 and 0.6%, CI (0.4, 0.8) in study MB102129).

The amount of missing data ranged between 5 and 10% across all studies. Missing data did not impact the results for the primary endpoint.

In all three studies, subjects from North America showed a smaller HbA1c reduction among subjects treated with saxa-dapa than subjects on the same treatment who were from Europe or Latin America. There is no clear explanation for the causes of this outcome.

5.3 Conclusions and Recommendations

Based on collective efficacy evidence provided in all three submitted studies, treatment with saxa-dapa combination resulted in larger HbA1c reduction at week 24 than saxa or dapa alone when given on background of metformin. Therefore, I would recommend the approval of this fixed dose combination if the safety profile of this drug meets FDA's requirements.

5.4 Labeling Recommendations

Update the text of section 14 of the label (b) (4)
Instead, I would suggest providing the intent-to-treat (de facto) estimands, which consider the actual measurements of subjects regardless of adherence to treatment or use of subsequent therapy. A pattern-mixture imputation approach could be used to obtain those estimands.

I recommend including information on dropout rates by treatment group. Also, I recommend including information on rates of retrieved dropouts.

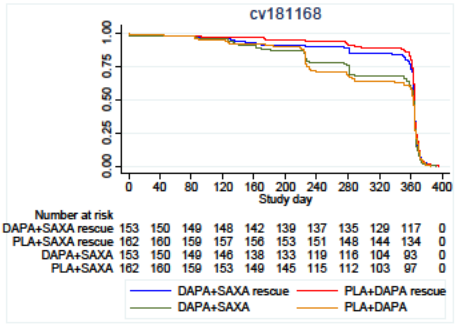
(b) (4)

I would recommend to rename the paragraph titled (b) (4) into "Known Proportion of patients achieving HbA1c<7%" in order to make it clear that there were no formal testing of this hypothesis, i.e. there was no Type I error adjustment in calculation of these results.

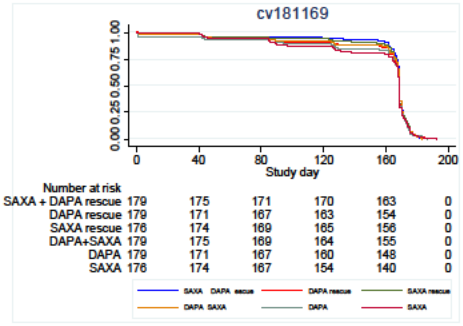
APPENDICES

Figure 13. Follow-up time: comparison of cohort with and without data after recue therapy

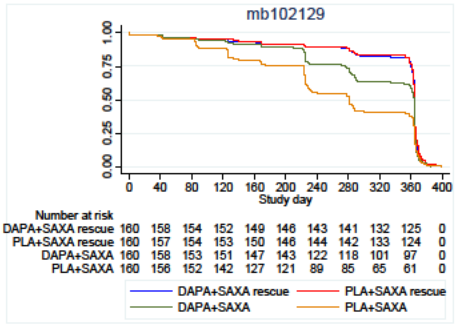
A



B



C



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

/s/

ANNA E KETTERMANN
01/04/2017

MARK D ROTHMANN
01/05/2017
I concur