

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205649Orig1s000

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 Memorandum

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 205649 / Sequence 0000

Drug Name: Dapagliflozin/ Metformin XR Fixed Dose Combination Tablets

Indication(s): To improve glycemic control in adults with type 2 diabetes mellitus

Applicant: Bristol-Myers Squibb

Date(s) Received: October 30, 2013

Review Priority: Standard (10-month)

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Wei Liu, Ph.D.

Concurring Reviewers: Mark Rothmann, Ph.D. (Team Leader)

Medical Division: Metabolism and Endocrinology Products

Clinical Team: Kaveeta Vasisht, M.D.
Karen M Mahoney, M.D. (Team Leader)

Project Manager: Elizabeth Chen

Keywords: NDA review, clinical studies, factorial design, labeling

1. SUMMARY

On 10/30/2013, Bristol-Myers Squibb (BMS, sponsor) Company submitted the initial New Drug Application (NDA) No. 205-649 for dapagliflozin (DAPA) + metformin extended-release (MET) fixed dose combination (FDC). This is a 505 (b2) submission. This application seeks marketing approval for the FDC of DAPA and MET (administered once daily [QD] to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). DAPA was studied under IND No. 68,652 when used as either monotherapy or in combination with other diabetes medicines, including MET, and bioequivalence studies to support the DAPA/MET FDC were conducted under IND 106,890.

The DAPA/MET FDC contains the following dosage forms:

- 10 mg DAPA/500 mg MET
- 10 mg DAPA/1000 mg MET
- 5 mg DAPA/500 mg MET
- 5 mg DAPA/1000 mg MET

There are data from 12 Phase 3 studies that support the efficacy and safety for the DAPA/MET FDC, all of which were previously submitted to the DAPA NDA 202-293. Selected studies were reviewed by Dr. Jonathan Norton. His review is dated September 8, 2011. Two of the 12 Phase 3 studies compared DAPA + MET to DAPA alone and to MET alone, respectively. These two studies are directly related to this application of DAPA/MET FDC and design aspects of these studies are briefly described in Table 1.

Table 1. Overview of Two Phase 3 Trials

Study ID (Brief Name)	Population	Dose (mg)	Background Tx (Rescue)	Comparator	Weeks
MB102021 (2021)	Drug-naïve with higher HbA1c	DAPA 5 mg + MET	None (Pioglitazone, acarbose, or sitagliptin)	DAPA 5 mg, MET	24
MB102034 (2034)	Drug-naïve with higher HbA1c	DAPA 10 mg + MET	None (Pioglitazone, acarbose, or sitagliptin)	DAPA 10 mg, MET	24

In both studies MET was dosed up to 2000 mg. In each study, the median MET dose was 2000 mg (the mean MET dose was less than 2000 mg).

Analyses by Dr. Jonathan Norton verified the sponsor's finding of MB102034 in his review. This reviewer further verified the results from MB102021 that appeared in the FARXIGA label (see Appendix). Results from these studies are summarized in Table 2. The primary analyses were based on similar ANOVA models using the last observation carried forward (LOCF) method for missing observations. Sensitivity analyses based on MMRM methods provided similar results as the corresponding primary analysis. The combination of DAPA + MET is superior to each component in the two studies based on the primary endpoint HbA1c change from baseline at Week 24.

Table 2: Change in HbA1c from Baseline at Week 24 by Treatment, Studies 2021 and 2034

	Treatment Arm					
	n	DAPA 5 mg + MET n=194	n	DAPA 5 mg n=203	n	MET n=201
Study 2021 [^]						
Adj. Mean (se)	185	-2.05 (.09)	196	-1.19 (.09)	195	-1.35 (.09)
Diff. from Combin.(se)		--		-.86 (.12)*		-.70 (.12)*
Completer	177	91.2%	170	83.7%	171	85.1%
Study 2034 [#]		DAPA 10 mg +MET n=211		DAPA 10 mg n=219		MET n=208
Adj. Mean (se)	202	-2.01 (1.08)	216	-1.44 (1.31)	203	-1.42 (1.41)
Diff. from Combin.(se)		--		.53 (.11)*		.54 (.11)*
Completer	183	86.7%	188	85.8%	181	87.0%

*p < .001 vs. the combination

[^] Source: study-mb102021-csr-final-24-week.pdf

[#] Source: study-mb102034-csr-final.pdf

Evaluation of Safety

The safety of DAPA/MET FDC was primarily reviewed by Kaveeta Vasisht, M.D.

Labelling Recommendations:

On the proposed changes to the product label:

1. The Farxiga label includes randomized studies of DAPA with MET. For the proposed label of FDC of DAPA/MET the sponsor wants to include (b) (4)

[Redacted]

Additionally, there are no new data of phase 3 clinical trials for supporting the DAPA/MET FDC. In such cases, it appears usual to include only that information on relevant studies that is provided in the Farxiga product label. This affects the following text which does not appear in the Farxiga product label:

- (in section 14.1, the last paragraph on page 43) (b) (4)

[Redacted]

- This statement was proposed for Farxiga labeling by the sponsor but was removed in the final version. This is because FDA requested that the Farxiga label to be consistent with the labeling of other SGLT2 inhibitors. These tests were pre-specified.

- (in section 14.1, the last paragraph on page 45) (b) (4)

[Redacted]

[Redacted] (b) (4)

- This statement was proposed for Farxiga labeling by the sponsor but was removed in the final version. This is because FDA requested that the Farxiga label to be consistent with the labeling of other SGLT2 inhibitors. These tests were pre-specified.

- [Redacted] (b) (4)

- This information was not provided in the Farxiga label [Redacted] (b) (4)

- [Redacted] (b) (4)

- It is not clear to which study or studies this statement refers. Additionally, there is no criterion to determine [Redacted] (b) (4), in any of the endpoints.

2. [Redacted] (b) (4)

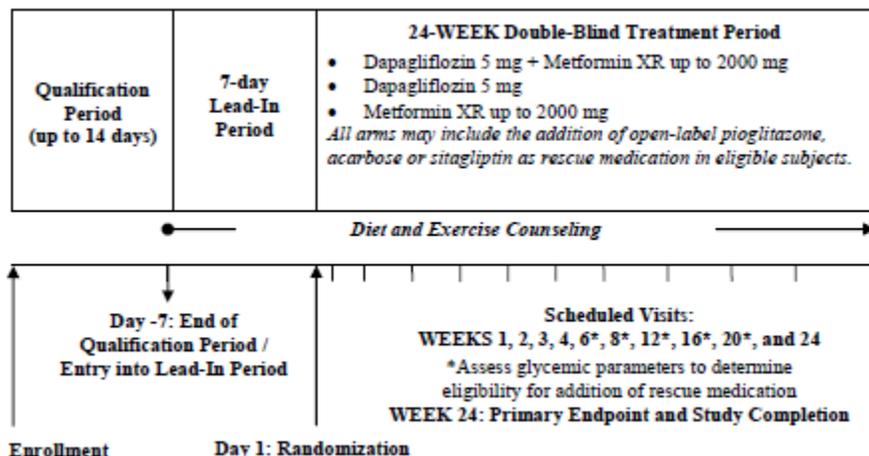
Appendix

MB102021 – Initial Combination with Metformin

Study Design and Endpoints

Study 2021 had a similar study design as that of study 2034. Figure 1 illustrates the design of Study 2021, which tested DAPA 5 mg in combination with metformin (MET). Patients were excluded if they had received more than 14 days of antihyperglycemic therapy (consecutive or not) in the previous 12 weeks.

Figure 1: Design of Study 2021



(Source: Clinical Study Report, study-mb102021-csr-final-24-week.pdf, Figure 3.1)

The primary efficacy endpoint was change in HbA1c at Week 24. In order for study to be deemed positive, the combination of DAPA 5 mg and MET had to be found statistically superior to each component. The secondary efficacy endpoints were similar to those in Study 2034.

Patient Disposition, Demographic and Baseline Characteristics

Of the 603 subjects randomized, 5 discontinued prior to taking any double-blind study medication; 3 subjects were lost to follow-up and 2 subjects withdrew consent.

Table 1: Disposition of Subjects and Primary Reason for not Completing the Double-blind Treatment Period (MB102021)

	Number (%) of Subjects			
	DAPA 5 MG + MET N = 194	DAPA 5 MG N = 203	MET N = 201	Total N = 598
Subjects completing the study	177 (91.2)	170 (83.7)	171 (85.1)	518 (86.6)
Subjects not completing the study	17 (8.8)	33 (16.3)	30 (14.9)	80 (13.4)
Reason for not completing the study				
Lack of efficacy	0	1 (0.5)	0	1 (0.2)
Adverse event	2 (1.0)	6 (3.0)	6 (3.0)	14 (2.3)
Subject withdrew consent	8 (4.1)	15 (7.4)	9 (4.5)	32 (5.4)
Death	0	1 (0.5)	0	1 (0.2)
Lost to follow-up	4 (2.1)	6 (3.0)	9 (4.5)	19 (3.2)
Poor/non-compliance	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Subject no longer meets study criteria	0	0	2 (1.0)	2 (0.3)
Other	2 (1.0)	3 (1.5)	3 (1.5)	8 (1.3)

(Source: Clinical Study Report, study-mb102021-csr-final-24-week.pdf, Table 1)

Table 2 shows the demographics of the subjects.

Table 2: Baseline and Demographic Characteristics

	DAPA 5 MG + MET N = 194	DAPA 5 MG N = 203	MET N = 201	Total N = 598
Age (yr)				
Mean	51.7	52.3	51.8	52.0
Median	51.0	53.0	52.0	52.0
Min, Max	28, 73	24, 76	22, 75	22, 76
Age Category (n, %)				
< 65 yr	177 (91.2)	183 (90.1)	184 (91.5)	544 (91.0)
≥ 65 and < 75 yr	17 (8.8)	17 (8.4)	16 (8.0)	50 (8.4)
≥ 75 yr	0	3 (1.5)	1 (0.5)	4 (0.7)
Gender (n, %)				
Male	78 (40.2)	92 (45.3)	95 (47.3)	265 (44.3)
Female	116 (59.8)	111 (54.7)	106 (52.7)	333 (55.7)
Race (n, %)				
White	153 (78.9)	166 (81.8)	158 (78.6)	477 (79.8)
Black/African-American	8 (4.1)	4 (2.0)	6 (3.0)	18 (3.0)
Asian	32 (16.5)	33 (16.3)	35 (17.4)	100 (16.7)
Other	1 (0.5)	0	2 (1.0)	3 (0.5)

(Source: Clinical Study Report, study-mb102021-csr-final-24-week.pdf, Table 2)

Statistical Methodologies

The statistical methods for this study were similar to that for study 2034. Randomization was stratified by site, with a block size of 3.

The primary analysis for the change in A1C from baseline to Week 24, or the last post-baseline measurement prior to Week 24 (if no Week 24 assessment is available), will be based on an analysis of covariance (ANCOVA) model, with treatment group as an effect and baseline value as a covariate.

The primary endpoint of change in A1C from baseline to Week 24 (LOCF) was assessed comparing dapagliflozin 5 mg plus metformin XR treatment group relative to the dapagliflozin 5 mg plus placebo treatment group and relative to the metformin XR plus placebo treatment group at the 0.05 significance level. Statistical significance will be claimed if the p-values for the comparisons between the dapagliflozin 5 mg plus metformin XR treatment group and both the dapagliflozin 5 mg plus placebo treatment group and the metformin XR plus placebo treatment group are < 0.05 two-sided.

The sample size is chosen to provide at least 90% power for the comparison of the combination arm versus the individual components based on the min test by Laska and Meisner for the normal case. One hundred and ninety subjects per treatment group are needed to detect a difference in means of 0.4% between dapagliflozin 5 mg plus metformin XR versus the individual components (ie, dapagliflozin 5 mg plus placebo and metformin XR plus placebo), assuming a standard deviation of 1.1%. Assuming that 5% of subjects do not have a post-baseline assessment, a total of 600 subjects (200 subjects per treatment arm) need to be randomized.

Results and Conclusions

Primary Efficacy Endpoint

Table 3 shows the results for primary efficacy endpoint. The combination of DAPA 5 mg and MET was superior to each component.

Table 3: Primary and Secondary Efficacy Endpoints at Week 24 (LOCF), Excluding Data After Rescue

EFFICACY ENDPOINT STATISTICS	DAPA 5MG + MET (N=194)	DAPA 5MG (N=203)	MET (N=201)
PRIMARY EFFICACY ENDPOINT			
HA1c (%) AT WEEK 24 (LOCF) N#	185	196	195
BASELINE MEAN (SD)	9.21 (1.305)	9.14 (1.374)	9.14 (1.317)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-2.05 (0.0892)	-1.19 (0.0866)	-1.35 (0.0868)
COMBINATION GROUP VS. DAPA 5MG			
DIFFERENCE (SE) (a)	-0.86 (0.1243)		
P-VALUE (*)	<.0001 *		
COMBINATION GROUP VS. MET			
DIFFERENCE (SE) (a)	-0.70 (0.1245)		
P-VALUE (*)	<.0001 *		
KEY SECONDARY EFFICACY ENDPOINTS IN HIERARCHICAL ORDER			
FPG (MG/DL) AT WEEK 24 (LOCF) N#	192	203	200
BASELINE MEAN (SD)	193.4 (55.78)	190.8 (56.49)	196.7 (59.93)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-61.0 (2.783)	-42.0 (2.708)	-33.6 (2.728)
COMBINATION GROUP VS. DAPA 5MG			
DIFFERENCE (SE) (a)	-19.1 (3.883)		
P-VALUE (*)	<.0001 *		
COMBINATION GROUP VS. MET			
DIFFERENCE (SE) (a)	-27.5 (3.897)		
P-VALUE (*)	<.0001 *		
KEY SECONDARY EFFICACY ENDPOINTS IN HIERARCHICAL ORDER			
SUBJECTS WITH HA1c<7.0% AT WEEK 24 (LOCF) X/N#	96/185	46/196	68/195
PERCENT	51.9%	23.5%	34.9%
PERCENT ADJUSTED FOR BASELINE HA1c (SE)	52.4% (3.581)	22.5% (2.741)	34.6% (3.296)
COMBINATION GROUP VS. DAPA 5MG			
DIFFERENCE (SE) (b)	29.9% (4.633)		
P-VALUE (*)	<.0001 *		
COMBINATION GROUP VS. MET			
DIFFERENCE (SE) (b)	17.8% (4.947)		
P-VALUE (*)	0.0003 *		

(Source: Clinical Study Report, study-mb102021-csr-final-24-week.pdf, Table 3)

Secondary Efficacy Endpoints

Table 3 also shows the results for FPG and body weight, which show the combination to be superior to each component.

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/s/

WEI LIU
06/17/2014

MARK D ROTHMANN
06/20/2014
I concur

STATISTICS FILING CHECKLIST FOR NDA/BLA

NDA Number: 205649/0000

Applicant: Bristol-Myers Squibb

Stamp Date: 10/30/2013

Drug Name:

NDA/BLA Type: New NDA

Dapagliglozin/Metformin XR FDC

On **initial** overview of the NDA/BLA application for RTF:

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			LOCF method

Comment: There were no new clinical trial data submitted in this NDA. No statistical comments to be sent to the sponsor in the 74-day letter.

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR NDA/BLA

Wei Liu

12/10/2013

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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/s/

WEI LIU
12/10/2013

MARK D ROTHMANN
12/10/2013
Concur