CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200678Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	200678/0000
Drug Name:	(b) (4)
Indication(s):	Treatment of Subjects with Type 2 diabetes
Applicant:	Bristol-Myers Squibb Company
Date(s):	Received 12/29/2009
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Wei Liu, Ph.D.
Concurring Reviewers:	J. Todd Sahlroot, Ph.D. (Deputy Director)
Medical Division:	Metabolism and Endocrinological Products (HFD-510, DMEP)
Clinical Team:	Arlet Nedeltcheva-Peneva, M.D. Hylton Joffe, M.D. (Team Leader) Mary Parks, M.D. (Division Director)
Project Manager:	Raymond Chiang

Keywords: NDA review, combination drug, active control/superiority, clinical studies

1. BACKGROUND

The coadministration of saxagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin alone and in treatment-naive patients inadequately controlled on diet and exercise alone. The applicant has submitted the results of 5 core Phase 1 studies in normal volunteers and 3 clinical phase 3 studies (CV181039, CV181014, and CV181066) in patients with type 2 diabetes also taking metformin. Data from the Onglyza NDA (22-350), approved by FDA on July 31, 2009, contribute largely to the clinical safety and efficacy data supporting this application. The phase 3 studies CV181039 and CV181014 were submitted as part of NDA 22-350 and were reviewed by Joy Mele, M.S., statistician in the Division of Biometrics 2. Study CV181066 was a 4-week, multicenter, randomized, double-Blind, placebo-controlled phase 3 trial to evaluate the efficacy and safety of saxagliptin in comparison to placebo as add-on treatment to metformin XR in subjects (N=93) with Type 2 diabetes who have inadequate glycemic control with diet and exercise and a stable dose of metformin XR $\geq$ 1500 mg/day. Based on the short 4-week treatment period and small number of patients involved, we view this study as a supportive study only. The sponsor is not proposing labeling for this study.

2. SUMMARY AND CONCLUSION

The efficacy of the coadministration of saxagliptin and metformin in this NDA submission is based on studies CV181039 (n=1306) and CV181014 (n=743) which were reviewed in NDA 22-350. In the proposed labeling of this submission, the sponsor is relying on the approval of Onglamet using the same clinical data. Material in the clinical studies section of label is identical to the relevant sections of the Onglamet label. Because there is no new relevant clinical efficacy data and the proposed label relies entirely on the previously submitted data, there is no compelling need for a statistical review of this NDA.

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/s/

WEI LIU
10/01/2010

JON T SAHLROOT
10/01/2010
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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 200678 **Applicant:** Bristol-Myers Squibb **Stamp Date: 12/29/2009**

Drug Name: Saxagliptin **NDA/BLA Type: New NDA**

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.)	✓			No ISS and ISE, but CV181038 and CV181066, respectively
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			
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.	✓			ANCOVA: treatment and baseline
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.	✓			Use the LOCF procedure

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