CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208658Orig1s000

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 MEMO

NDA/BLA #:	NDA 208658
Drug Name:	Synjardy XR (Empagliflozin and Metformin Hydrochloride Extended-Release tablets)
Indication(s):	Improve glycemic control in adults with type 2 diabetes mellitus
Applicant:	Boehringer Ingelheim
Date(s):	Stamp: February 10, 2016 Review due date: November 4, 2016 PDUFA: December 9, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometric II
Statistical Reviewer:	Shuxian Sinks, PhD
Concurring Reviewers:	Mark Rothmann, PhD, Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Andreea Lungu, MD, Medical Reviewer William Chong, MD, Diabetes Team Leader
Project Manager:	Michael White, PhD

1 EXECUTIVE SUMMARY

1.1 Brief Overview

Boehringer Ingelheim submitted this application for the fixed-dose combination (FDC) of empagliflozin and metformin hydrochloride extended-release (XR) for the treatment of adults with type 2 diabetes mellitus. The applicant is seeking for approval for the indications:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

(b) (4)

Synjardy (empagliflozin/metformin hydrochloride IR FDC) was approved on August 25, 2015 for the use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin. (b) (4) The approved strengths of Synjardy were: 5 mg empagliflozin/ 500 mg metformin hydrochloride, 5 mg empagliflozin/1000 mg metformin hydrochloride, 12.5 mg empagliflozin/ 500 mg metformin hydrochloride, 12.5 mg empagliflozin/ 1000 mg metformin hydrochloride.

The applicant proposed four table strengths of empagliflozin/metformin XR FDC for labeling claim: 5 mg empagliflozin/1000 mg metformin hydrochloride extended-release, 10 mg empagliflozin/1000 mg metformin hydrochloride extended-release, 12.5 mg empagliflozin/1000 mg metformin hydrochloride extended-release, 25 mg empagliflozin/1000 mg metformin hydrochloride extended-release.

No new efficacy data were included to evaluate the efficacy of empagliflozin/metformin XR FDC. The applicant made cross-reference to Jardiance (empagliflozin, NDA 204629), and Glumetza (metformin XR, NDA 021748), and Synjardy (the combination of empagliflozin/metformin IR, NDA 206111).

1.2 Study Results

There were no new efficacy studies included in this submission.

1.3 LABELING

I compared the proposed Synjardy XR labeling with current approved Synjardy labeling. (b) (4)

(b) (4)

(b) (4). There were no new clinical studies investigating the efficacy of empagliflozin/metformin XR FDC included in the proposed Synjardy XR label. In addition, there were no changes to the study descriptions or to the presentation of the study results that appear in the proposed Synjardy XR label.

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

/s/

SHUXIAN Z SINKS
11/03/2016

MARK D ROTHMANN
11/03/2016
I concur

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 208658
Product Name:	Synjardy® XR (empagliflozin and metformin extended release)
Indication(s):	patients with Type II diabetes
Applicant:	Boehringer Ingelheim
Dates:	PDUFA goal date : December 10 , 2016
Review Priority:	Standard
Biometrics Division:	Division II
Statistical Reviewer:	Shuxian Sinks, PhD
Concurring Reviewers:	Mark Rothmann, PhD, Team Leader
Medical Division:	Department of Metabolism and Endocrinology Products
Clinical Team:	Bill Chong, MD, Team Leader
Project Manager:	Michael White, PhD

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

This application does not include new clinical data to investigate the efficacy of empagliflozin/metformin XR fixed dose combination (FDC) as agreed with the Agency. (b) (4)

(b) (4)

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments

Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	Yes
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	NA
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	No

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	NA
Were analysis datasets provided?	No
Dataset structure (e.g., SDTM or ADaM)	NA
Are the define files sufficiently detailed?	NA
List the dataset(s) that contains the primary endpoint(s)	NA
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	NA
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	NA
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	NA

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols,			X	

Content Parameter	Yes	No	NA	Comments
subsequent amendments, etc.)				
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).			X	No data is submitted for this application to review
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

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

/s/

SHUXIAN Z SINKS
04/08/2016

MARK D ROTHMANN
04/08/2016
I concur