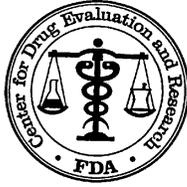


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204353Orig1s000

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 Serial Number: NDA 204353/ Sequence 0000

Drug Name: Canagliflozin/Metformin Immediate Release Fixed Dose
Combination oral tablets (proposed tradename (b) (4))

Indication(s): To improve glycemic control in adults with type 2 diabetes
mellitus as an adjunct to diet and exercise

Applicant: Janssen Research & Development, LLC

Date received: December 12, 2012

Review Priority: Standard (10-month)

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Wei Liu, Ph.D.

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

Medical Division: Metabolism and Endocrinology Products

Clinical Team: Hyon Kwon, M.D.
Jean-Marc Guettier, M.D. (Acting Director)

Project Manager:

Keywords: NDA review, clinical studies, labeling, bootstrap

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1. EXECUTIVE SUMMARY

1.1. INTRODUCTION

The sponsor (Janssen Pharmaceuticals, Inc.) submitted an original NDA for Canagliflozin (JNJ-28431754) and Metformin Hydrochloride (JNJ-1158196) Immediate Release Fixed Dose Combination (CANA/MET IR FDC) oral tablets (50/500, 50/1000, 150/500, 150/1000 mg) to be marketed as a prescription product for the treatment of type 2 diabetes mellitus (T2DM). This application relies on data submitted in the canagliflozin NDA 204042 (I reviewed the efficacy) and in the Glucophage NDA 20357. Therefore, there was no new phase 3 data in this application, except the data of new Phase 1 and 2 studies.

In addition to the label review, there is a review issue in this submission due to dosing regimens. The metformin dosing needs twice daily for T2DM patients, leading to the requirement of FDC dosing twice daily or equivalently CANA dosing twice daily. To reach a total daily CANA dose of 100 mg and 300 mg, respectively, the sponsor developed CANA/metformin IR FDC as 50/500, 50/1000, 150/500, 150/1000 mg. In the phase 2 efficacy study DIA2003, the sponsor compared the efficacy of twice daily cana (50 and 150 mg twice daily) to placebo as add-on to metformin at 18 weeks. Unfortunately, in this study, they did not have once daily dosing group. The sponsor stated that there was a phase 3 study DIA3006 which was submitted in NDA204042 had a similar design of DIA2003 with regard to study enrollment criteria but mainly differed in the duration of the double-blind treatment period (18 weeks and 26 weeks for DIA2003 and DIA3006, respectively). In study DIA3006, the efficacy of canagliflozin 100 mg and 300 mg daily as add-on to metformin versus placebo was evaluated. Therefore, the sponsor tried to bridge the twice daily (study DIA2003) and once daily (study DIA3006) dosing in order to demonstrate that twice daily dosing will have similar glycemic efficacy as daily dosing. However, there do not appear to be an exposure-response relationship for plasma canagliflozin concentrations and HbA1C response for canagliflozin from the PK and PD analyses. In absence of an exposure-response relationship, it is not clear how the efficacy/safety data from the once-daily dosing are bridged with the proposed twice-daily dosing for the fixed dose combination (FDC).

Compared to DIA3006, the HbA1c lowering seen in DIA2003 was smaller when one compares the treatment arms with same total daily dose of canagliflozin. The sponsor attributed this to the difference in baseline HbA1c between two studies, and conducted a simulation study using the Bootstrap algorithm to assess the potential impact of baseline glycemic control on the primary efficacy analysis.

1.2 STATISTICAL SUMMARY

Statistical Comments to Bootstrap Simulation for Bridging Dosing

Our statistical comments were carried to the sponsor in the Mid-Cycle communication dated on 5/29/2013:

“We note that you used a bootstrap method to bridge QD dosing in Study DIA3006 and BID dosing in Study DIA2003. We have several reservations. Your analysis is post-hoc, and as such is subject to the usual limitations of analyses conducted with the data in-hand. Secondly, cross-trial comparisons are difficult to interpret. Finally, your method uses the observed baselines in the two studies to reconcile between-study differences in HbA1c. While HbA1c baseline differences represent an important aspect of the two studies, there may be many other factors that also influence HbA1c.”

If there were no PD/PK data supporting the bridging, a simulation (bootstrap) study probably won't do it either. Bootstrap is a perfectly good statistical technique but it doesn't mean good in drug regulation. The sponsor called the simulation study "supplemental". However, we viewed it as exploratory with an attempt to "rescue" the failed PK/PD results.

The sponsor's bootstrap procedure only accounts for a single known prognostic factor. It does not account for other known or unknown prognostic factors, or for environmental/study differences between the two studies. This is a common issue with any across trials comparison. Their bootstrap procedure is not a substitute for a comparison in a randomized study.

Additional concern is that there is no control on error associated to the two independent studies.

Confirmation of Efficacy in Add-on Combination Therapy with Insulin (with or Without Other Anti-Hyperglycemic Agents, Including Metformin)

This reviewer verified the sponsor's results of the superiority of canagliflozin 300 mg and 100 mg doses vs. placebo in HbA1c change from baseline, the primary efficacy endpoint, in a subgroup population (Study DIA3008 population 3) of the add-on combination therapy with insulin (with or without other anti-hyperglycemic agents, including metformin) was significant at level of $\alpha=0.05$. The results were based on LOCF as the primary method for accounting for missing data. Analyses using MMRM performed by this reviewer were consistent with the primary results with LOCF.

Statistical Comments to the proposed label:

1. Section 14.6 second paragraph line 10, change

“...in systolic blood pressure relative to placebo was -3.5 mmHg and -6 mmHg with”

to

“...in systolic blood pressure relative to placebo was -3.1 mmHg and -5.9 mmHg with”

2. Section 14.6 second paragraph line 12-14, the text was

“... required glycemic rescue therapy: 3.6% of patients receiving canagliflozin 100 mg, 2.7% of patients receiving canagliflozin 300 mg, and 6.2% of patients receiving placebo ...”

However, the percentages of rescued patients from my calculation are:

3.6% of patients (5/139) receiving canagliflozin 100 mg, 4.7% of patients(7/148) receiving canagliflozin 300 mg, and 8.3% of patients (12/145) receiving placebo

I defer to the clinical on whether “rescued” and “glycemic rescued” are meaningfully different.

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/s/

WEI LIU
09/05/2013

THOMAS J PERMUTT
09/05/2013
concur

MARK D ROTHMANN
09/05/2013
I concur

STATISTICS FILING CHECKLIST FOR NDA/BLA

NDA Number: 204353/0000 **Applicant:** Janssen

Stamp Date: 12/12/2012

Drug Name: Canagliflozin/Metformin IR **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.)	✓			
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.	✓			
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 is no new phase 3 data in the application. In addition to new Phase 1 and 2 studies, this application relies on data submitted in the canagliflozin NDA 204-042 (under review) and in the Glucophage® NDA 20-357.

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR NDA/BLA

No statistical review issues to be forwarded to the Applicant for the 74-day letter.

Wei Liu

1/25/2013

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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/s/

WEI LIU
02/21/2013

JON T SAHLROOT
02/21/2013

STATISTICS FILING CHECKLIST FOR NDA/BLA

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Stamp Date: 12/12/2012

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Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
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Wei Liu

1/25/2013

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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/s/

WEI LIU
01/25/2013

JON T SAHLROOT
01/25/2013