

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205879Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205879

SUPPL #

HFD # 510

Trade Name Invokamet XR

Generic Name canagliflozin and metformin hydrochloride extended release tablets

Applicant Name Janssen Pharmaceuticals, Inc.

Approval Date, If Known September 20, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Approvability of this NDA required review of bioavailability/bioequivalence data. Please see page 8 of 58 from the Clinical Pharmacology review, uploaded into DARRTS on August 16, 2016.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product. N/A

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 204353	Invokamet (cangliflozin and metformin hydrochloride immediate release) tablets
NDA# 204042	Invokana (canagliflozin) tablets
NDA# 021748	Glumetza (metformin hydrochloride extended release) tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete

remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in

that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Elizabeth Godwin
Title: Regulatory Project Manager
Date: September 20, 2016

Name of Office/Division Director signing form: Jean-Marc Guettier, MD
Title: Director, Division of Metabolism and Endocrinology Products

(Lisa Yanoff, MD signing on behalf of Jean-Marc Guettier)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ELIZABETH R GODWIN
09/20/2016

LISA B YANOFF
09/20/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205879	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Invokamet XR Established/Proper Name: canagliflozin and metformin hydrochloride extended-release Dosage Form: Tablets		Applicant: Janssen Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Elizabeth Godwin, MSHS, CCRP		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____ <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>	
❖ Actions		
- Proposed action - User Fee Goal Date is <u>September 20, 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		Not Applicable ☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 4 – New Combination
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	☐ Yes ☐ No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval: September 20, 2016
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (refer to labeling attached to approval letter)
• Original applicant-proposed labeling	☒ Included (original draft label text from 11/20/2015)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (refer to labeling attached to approval letter)
• Original applicant-proposed labeling	☒ Included (original draft med guide submitted 11/20/2015)
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	☒ Included (refer to labels attached to approval letter)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	January 25, 2016 January 17, 2016
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: ☒ January 20, 2016 DMEPA: ☒ September 2, 2016, August 4, 2016 DMPP/PLT (DRISK): ☒ August 23, 2016 OPDP: ☒ September 6, 2016 SEALD: None CSS: None Product Quality ☒ See product quality review Other: ☒ DPMH May 15, 2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM filing review: January 20, 2016 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	☒ No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☒ None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None September 20, 2016
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	September 16, 2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See page 13 of clinical review dated September 16, 2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None August 12, 2016, January 14, 2016

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None August 16, 2016, January 13, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☐ None requested March 8, 2016
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None May 31, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	☒ None Not applicable
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ None Not applicable
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	☐ None August 17, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
☒ Review & FONSI <i>(indicate date of review)</i>	August 17, 2016
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change))</i>	☒ Acceptable Re-evaluation date: N/A ☐ Withhold recommendation ☒ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>) Not Applicable
• Finalize 505(b)(2) assessment	☐ Done Not Applicable
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done Not Applicable (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done Not Applicable
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done Not Applicable
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

ELIZABETH R GODWIN
09/21/2016

From: [Godwin, Elizabeth](#)
To: [Porter, Brandon \[JRDUS\]](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Date: Tuesday, September 20, 2016 2:00:13 PM
Attachments: [CanaMet XR FDC USPI - Clean- 20Sep2016.docx](#)
[image001.png](#)

Hi Brandon,

We accept your revisions dated September 20, 2016.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Tuesday, September 20, 2016 12:15 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, we accepted all the Agency's changes and have added a couple minor edits. I have included a clean and marked version.

Let me know if you have any questions.

Best,

Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, September 19, 2016 2:37 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Importance: High

Hi Brandon,

Please see the attached label with FDA comments for NDA 205879. Please send the revised label back as soon as possible.

Please confirm receipt.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [<mailto:BPor3@its.jnj.com>]
Sent: Monday, September 19, 2016 2:53 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, we have accepted all the Agency's changes in this latest version and updated a couple dates in the document. I have included a clean final version and a Marked version.

Please let me know if you need anything further.

Best,
Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Friday, September 16, 2016 2:49 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Importance: High

Hi Brandon,

Please see the attached label with FDA comments for NDA 205879. Please send the revised label back as soon as possible.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

Please confirm receipt of this email.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [<mailto:BPor3@its.jnj.com>]
Sent: Tuesday, September 13, 2016 3:57 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, please find our comments in the attached USPI.
Best,
Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, September 12, 2016 12:49 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Brandon,

Thanks for the update, submitting the label tomorrow is fine.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Monday, September 12, 2016 3:19 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, we are working hard to finalize our response, but it looks like we will need one more day. Could we send you our response tomorrow?
Sorry for any inconvenience, but we want to make sure we get it right.
Best,
Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Wednesday, September 07, 2016 11:33 AM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hello Brandon,

Please see the attached label with FDA comments for NDA 205879. We request that you send the revised labeling by COB Monday, September 12, 2016.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

Please confirm receipt of this email.

If you have any questions, please contact me.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Tuesday, August 23, 2016 1:57 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, please see the attached USPI containing only tracked changes as described below. It does include the S-020 text changes regarding fatal DKA as well. Please let me know if you have any questions.
Best,
Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Wednesday, August 17, 2016 1:48 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hello Brandon,

Please see the attached label with FDA comments for NDA 205879. We request that you send the revised labeling by COB Wednesday, August 24, 2016.

In your response for, please incorporate the changes from the recently approved NDA 204353/S-020 (Invokamet) label from August 17, 2016.

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Please confirm receipt of this email.

If you have any questions, please contact me.

Thanks,
Liz

Liz Godwin, MSHS, CCRP | Regulatory Project Manager | Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II | Office of New Drugs | Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue, WO22, Room 3361 | Silver Spring, MD 20993

☎ 240.402.3438 (phone)

✉ Elizabeth.Godwin@fda.hhs.gov

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/s/

ELIZABETH R GODWIN
09/20/2016

From: [Porter, Brandon \[JRDUS\]](#)
To: [Godwin, Elizabeth](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Date: Friday, September 16, 2016 7:11:33 PM
Attachments: [emfinfo.txt](#)

Pages from 43 to 51 of this document are missing in the scanned package. Based on the content and the serial number of the sections, I have

complete this note

Hi Liz, I confirm receipt. We will respond as soon as possible.

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Friday, September 16, 2016 2:49 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Importance: High

Hi Brandon,

Please see the attached label with FDA comments for NDA 205879. Please send the revised label back as soon as possible.

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Please confirm receipt of this email.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.inj.com>]
Sent: Tuesday, September 13, 2016 3:57 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, please find our comments in the attached USPI.
Best,
Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, September 12, 2016 12:49 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Brandon,

Thanks for the update, submitting the label tomorrow is fine.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Monday, September 12, 2016 3:19 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, we are working hard to finalize our response, but it looks like we will need one more day. Could we send you our response tomorrow?
Sorry for any inconvenience, but we want to make sure we get it right.
Best,
Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Wednesday, September 07, 2016 11:33 AM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hello Brandon,

Please see the attached label with FDA comments for NDA 205879. We request that you send the revised labeling by COB Monday, September 12, 2016.

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Please confirm receipt of this email.

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Thanks,
Liz

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Tuesday, August 23, 2016 1:57 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, please see the attached USPI containing only tracked changes as described below. It does include the S-020 text changes regarding fatal DKA as well.

Please let me know if you have any questions.

Best,
Brandon

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Wednesday, August 17, 2016 1:48 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hello Brandon,

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Office of Drug Evaluation II | Office of New Drugs | Center for Drug Evaluation and Research
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/s/

ELIZABETH R GODWIN
09/19/2016

From: [Porter, Brandon \[JRDUS\]](#)
To: [Godwin, Elizabeth](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Date: Monday, September 19, 2016 5:39:10 PM
Attachments: [emfinfo.txt](#)

I confirm receipt. Thanks Liz

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Monday, September 19, 2016 2:37 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Importance: High

Hi Brandon,

Please see the attached label with FDA comments for NDA 205879. Please send the revised label back as soon as possible.

Please confirm receipt.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [mailto:BPor3@its.jnj.com]
Sent: Monday, September 19, 2016 2:53 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, we have accepted all the Agency's changes in this latest version and updated a couple dates in the document. I have included a clean final version and a Marked version.

Please let me know if you need anything further.

Best,
Brandon

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Friday, September 16, 2016 2:49 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Importance: High

Hi Brandon,

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Sent: Tuesday, September 13, 2016 3:57 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Liz, please find our comments in the attached USPI.
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From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, September 12, 2016 12:49 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

Hi Brandon,

Thanks for the update, submitting the label tomorrow is fine.

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Sent: Monday, September 12, 2016 3:19 PM
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Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

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Sorry for any inconvenience, but we want to make sure we get it right.
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From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]

Sent: Wednesday, September 07, 2016 11:33 AM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

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Sent: Tuesday, August 23, 2016 1:57 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

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Sent: Wednesday, August 17, 2016 1:48 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: NDA 205879 - canagliflozin/metformin extended release - Labeling

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ELIZABETH R GODWIN
09/19/2016

From: [Godwin, Elizabeth](#)
To: [Porter, Brandon \[JRDUS\]](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling
Date: Wednesday, September 07, 2016 2:32:53 PM
Attachments: [NDA 205879 XR FDC USPI - Marked - FDA comments 07Sept2016.docx](#)

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Sent: Tuesday, August 23, 2016 1:57 PM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - canagliflozin/metformin extended release - Labeling

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Brandon

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Sent: Wednesday, August 17, 2016 1:48 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: NDA 205879 - canagliflozin/metformin extended release - Labeling

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ELIZABETH R GODWIN
09/07/2016

From: [Godwin, Elizabeth](#)
To: [Porter, Brandon \[JRDUS\]](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: NDA 205879 - canagliflozin/metformin extended release - Labeling
Date: Wednesday, August 17, 2016 4:47:50 PM
Attachments: [NDA 205879 draft-annot-labeling-text FDA comments 17August2016.doc](#)

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ELIZABETH R GODWIN
08/17/2016

From: [Porter, Brandon \[JRDUS\]](#)
To: [Godwin, Elizabeth](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: RE: NDA 205879 - canagliflozin/metformin XR - Information Request
Date: Tuesday, August 16, 2016 11:47:05 AM
Attachments: [emfinfo.txt](#)

I confirm receipt Liz. Thank you.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 8:42 AM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: NDA 205879 - canagliflozin/metformin XR - Information Request

Hello Brandon,

We have the following comment regarding the carton and container labels, submitted on November 20, 2015, for NDA 205879.

We recommend the following be implemented prior to approval of this NDA:

- A. Professional Sample Container Labels
 - 1. Increase the size and prominence of the "Sample-Not for Sale" statement so that it is clear that these are drug samples, per 21CFR 203.38(c).

Please submit the revised carton and container labels by Friday, August 26, 2016.

Please confirm receipt of this email.

Thanks,
Liz

Liz Godwin, MSHS, CCRP | Regulatory Project Manager | Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II | Office of New Drugs | Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue, WO22, Room 3361 | Silver Spring, MD 20993
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/s/

ELIZABETH R GODWIN
08/16/2016

**PeRC Meeting Minutes
August 3, 2016**

PeRC Members Attending:

Lynne Yao

Gettie Audain

Thomas Smith

Meshaun Payne

Wiley Chambers

George Greeley

Barbara Buch

Adrienne Hornatko-Munoz

John Alexander

Gettie Audain

Dianne Murphy

Lily Mulugeta

Kevin Krudys

Julia Pinto

Gil Burkhart

Dionna Green

Raquel Tapia

Hari Cheryl Sachs

Gerri Baer

Rosemary Addy

Maura O'Leary

Agenda

NON-RESPONSIVE

10:55	NDA 205879	Invokamet XR (canagliflozin/ metformin HCL) Extended Release FDC Tablets (Partial Waiver/Deferral/Plan) with Agreed iPSP	DMEP	Bola Adeolu	An adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate.

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NON-RESPONSIVE

Invokamet XR (Canagliflozin/ Metformin Hcl) Extended Release FDC Tablets (Partial Waiver/Deferral/Plan) with Agreed iPSP

- Approved Indication: An adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate.
- This product triggers PREA as a new active ingredient (new combination product) and has a PDUFA goal date of September 20, 2016.
- The division clarified that the PREA PMRs already established for canagliflozin are being conducted using a background of either metformin IR or metformin ER.

Therefore, the studies being conducted for canagliflozin can also be used to support any PREA requirements for this combination product.

- *PeRC Recommendations:*
 - The PeRC agreed with the sponsor's plan for a partial waiver in patients 0 to less than 10 years of age because the studies are impossible and highly impractical and to a deferral in patients 10 years to 17 years of age.
 - The PeRC agreed that the PMRs for canagliflozin already established can be used to fulfill PREA PMRs for this product (see discussion above).

NON-RESPONSIVE

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/s/

GETTIE AUDAIN
08/17/2016

From: [Porter, Brandon \[JRDUS\]](#)
To: [Godwin, Elizabeth](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: RE: NDA 205879 - Canagliflozin/Metformin Hydrochloride Extended Release - Information Request
Date: Tuesday, May 10, 2016 5:11:54 PM
Attachments: [emfalert.txt](#)

Hi Liz, I confirm receipt.

Best,
Brandon

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Tuesday, May 10, 2016 12:16 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - Canagliflozin/Metformin Hydrochloride Extended Release - Information Request

Hi Brandon,

You have clarified that the starting dose for patients not treated with either canagliflozin or metformin is intended to be 'two' INVOKAMET XR tablets containing canagliflozin 50 mg and metformin 500 mg. Please justify and provide supporting data for starting metformin 1000 mg daily (total dose) in treatment naïve patients.

Please confirm receipt of this email.

Thanks,
Liz

From: Porter, Brandon [JRDUS] [mailto:BPorter3@its.inj.com]
Sent: Tuesday, May 10, 2016 11:48 AM
To: Godwin, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 205879 - Canagliflozin/Metformin Hydrochloride Extended Release - Information Request

Hi Liz, after discussing with the team, it appears that this was an oversight and should read as follows:

- Section 2.2, Recommended Dosage: "In patients currently not treated with either canagliflozin or metformin, initiate therapy with two INVOKAMET XR tablets containing canagliflozin 50 mg and metformin 500 mg;"

Let me know if you need anything further.
Best,
Brandon

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]

Sent: Thursday, May 05, 2016 5:22 AM

To: Porter, Brandon [JRDUS]

Cc: Saran, Sukhdev [JRDUS]

Subject: NDA 205879 - Canagliflozin/Metformin Hydrochloride Extended Release - Information Request

Hello Brandon,

We have the following question with reference to your proposed dosing statement

(b)(4)

(b)(4)

(b)(4)

If yes, what are the

supporting data for starting

(b)(4)

Please submit your response to the NDA by Wednesday, May 11, 2016.

Please confirm receipt of this email.

Thanks,

Liz

Liz Godwin, MSHS, CCRP | Regulatory Project Manager | Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II | Office of New Drugs | Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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✉ Elizabeth.Godwin@fda.hhs.gov

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/s/

ELIZABETH R GODWIN
05/11/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205879

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Janssen Pharmaceuticals, Inc.
3210 Merryfield Row
San Diego, CA 92121

ATTENTION: Brandon D. Porter
Associate Director, Global Regulatory Affairs

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) dated and received, November 20, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Canagliflozin and Metformin Hydrochloride Extended Release Tablets, 50 mg/500 mg, 50 mg/1,000 mg, 150 mg/500 mg, and 150 mg/1,000 mg.

We also refer to your correspondence, dated and received December 9, 2015, requesting review of your proposed proprietary name, Invokamet XR.

We have completed our review of the proposed proprietary name, Invokamet XR and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 9, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Abolade Adeolu, Senior Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
01/25/2016



NDA 205879

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Brandon Porter
Associate Director, Global Regulatory Affairs
3210 Merryfield Row
San Diego, CA 92121

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) dated November 20, 2015, received November 20, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for canagliflozin and metformin hydrochloride extended-release tablets, 50/500 mg, 50/1000 mg, 150/500 mg, and 150/1000 mg.

We also refer to your amendments dated December 9 and 17, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 20, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **August 23, 2016**.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

During our preliminary review of your submitted labeling you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information on canagliflozin and metformin hydrochloride tablets use in pregnant and lactating women by March 1, 2016:

- a review and summary of all available published literature regarding canagliflozin and metformin XR hydrochloride, this should be a review and summary of all available published literature regarding both individual components,
- a review and summary from your pharmacovigilance database,
- interim ongoing or final report on a closed pregnancy registry (if applicable),
- a revised labeling, if appropriate, incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request and/or partial deferral request is denied.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
01/20/2016



NDA 205879

NDA ACKNOWLEDGMENT

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Brandon Porter
Associate Director, Global Regulatory Affairs
3210 Merryfield Row
San Diego, CA 92121

Dear Mr. Porter:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: canagliflozin and metformin hydrochloride extended-release tablets, 50/500, 50/1000, 150/500, 150/1000 mg

Date of Application: November 20, 2015

Date of Receipt: November 20, 2015

Our Reference Number: NDA 205879

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 19, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu, RPh, MS, MBA
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ABOLADE ADEOLU
11/23/2015



IND 110533

**MEETING REQUEST-
WRITTEN RESPONSES**

Janssen Research & Development, L.L.C
Attention: Sukhdev K. Saran, Global Regulatory Affairs
920 U.S. Highway 202 P.O Box 300
Raritan, NJ 08869

Dear Ms. Saran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-28431754 (canagliflozin).

We also refer to your submission dated June 12, 2014, containing meeting request. The purpose of the requested meeting was to discuss proposed content of the CMC portion of the NDA 205879

Further reference is made to our Meeting Granted letter dated June 24, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your July 16, 2014 background package.

If you have any questions, call Priyanka Kumar, Regulatory Project Manager, at (240) 402-3722.

Sincerely,

{See appended electronic signature page}

Danae Christodoulou, Ph.D.
Branch Chief (Acting)
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: 110533
Product Name: JNJ-28431754 (canagliflozin).
Indication: **Treatment of Type 2 Diabetes Mellitus**
Sponsor/Applicant Name: Janssen Research and Development LLC

1.0 BACKGROUND

Janssen Research & Development (JRD) has developed canagliflozin (Cana), a sodium glucose co-transporter 2 (SGLT2) inhibitor, for the treatment of type 2 diabetes mellitus. NDA 204042 for Invokana® (canagliflozin immediate release tablets 100 and 300 mg/tablet) was approved on 29 March 2013. JRD is also developing canagliflozin combination dosage forms with immediate release (IR) and extended release (XR) metformin hydrochloride (Met). Canagliflozin/metformin hydrochloride immediate-release, fixed-dose combination (Cana/Met IR FDC) tablets are the subject of pending NDA 204353. Canagliflozin/metformin hydrochloride extended release fixed dose combination (Cana/Met XR FDC) tablets are currently under development and are the subject of this background package. The primary objective of this Type C meeting is to obtain agreement with the United States(US) Food and Drug Administration (FDA), (hereafter referred to in this document as the Agency) regarding the proposed content of the Chemistry, Manufacturing and Controls section of the CANA/MET XR FDC New Drug Application (NDA) (205879) to be submitted in January 2015 by Janssen Research and Development, LLC (JRD) on behalf of Janssen Pharmaceuticals, Inc., (hereafter referred to in this document as the “sponsor” or “JRD”). On 18 September 2013, a request for a Type B pre-NDA meeting was submitted to IND110533 (Serial No. 277). On 18 October 2013, a briefing book containing general background information on the Cana/Met XR FDC tablet formulation and manufacturing process, as well as additional rationale regarding the company's proposals with regard to the topics covered in each of the 6 CMC questions was submitted.

2.0 QUESTIONS AND RESPONSES

2.1. Category/Discipline A

Question 1: As agreed at the 30 August 2010 End of Phase 2 (EOP2) meeting, JRD conducted an alcohol induced dose-dumping study. In its 25 November 2013 written response to JRD’s Pre-NDA CMC questions, the Agency requested that JRD discuss the results of this study before submitting the Cana/Met XR FDC NDA. The results of this study are included in this Briefing Book.

Does the Agency agree that the outcome of this study is sufficient for evaluation to demonstrate the absence of “dose dumping” for the Cana/Met XR FDC tablets?

Does the Agency agree that the outcome of this study is sufficient to demonstrate the absence of “dose dumping” for the Cana/Met XR FDC tablets?

FDA Response to Question 1: *We note that there is a significant decreasing trend in the dissolution profiles using 40% ethanol in 0.1 N HCl. Provide an explanation for this observed decrease. We recommend that you discuss the potential impact of this decrease on efficacy with the Division of Metabolism and Endocrinology Products.*

Question 2: Does the Agency agree that the required 3 process validation batches of each strength may be manufactured as listed in Table 3 using a combination of metformin HCl granulate from both proposed granulate manufacturing facilities (Janssen Ortho, LLC ^{(b) (4)} [REDACTED]) to validate the use of metformin HCl granulate from either of these sources?

FDA Response to Question 2: *Yes, we agree with your proposal to manufacture the process validation batches of each dosage strength using the metformin HCl granulate from both proposed commercial sites (Janssen Ortho, LLC, ^{(b) (4)} [REDACTED]).*

Question 3: Does the Agency agree with our proposal to use the NIR method on the tablet cores to determine CU of canagliflozin in the CANA/MET XR FDC tablets as a quality control (QC) release method?

FDA Response to Question 3: *The Agency supports the use of modern analytical techniques for quality control of drug products. Although your description of proposed NIR implementation lacks details for full evaluation, it allows us to identify areas of concern as follows:*

- *It is not clear why you propose to use the correction factor. Since NIR is based on the reference UHPLC methods used also for assay determination, these two methods should be equivalent and according to USP the correction should not be used. In addition it is noted that USP allows for a single factor, while you seem to propose a different factor for each analysis. Please provide more information on why the correction is necessary for the analysis.*
- *Reported preliminary results and validation acceptance criteria show that standard error of prediction may be higher than 5%. You should provide a strong justification of suitability of the method for CU measurement.*
- *You propose to repeat testing by UHPLC when the NIR correction factor is outside limit of 0.9 – 1.1 and NIR method is judged not fit for the intended purpose. This approach of repeating test by alternative method when the routine method fails is not acceptable. The first failure should open an investigation, and the alternative testing can be done only as a part of this investigation.*

Regarding the proposed specification; you propose to designate NIR as the primary method, and UHPLC as the alternate method. This terminology is confusing. You need to indicate that NIR

will be used as the routine method, and UHPLC as the alternative. You also need to designate UHPLC as the regulatory method.

Additional comments:

- *It is expected that the submission will include comprehensive description of the calibration development, including description of data sets, wavelength ranges, method use to establish the number of factors, etc.*
- *It is the agency's expectation that details of model maintenance will be available on site for evaluation during an inspection; however an overview of model maintenance is expected in the application to allow complete evaluation of the NIR procedure.*
- *You should evaluate effect of tablet hardness, (b) (4) and tablet core orientation in the holder on NIR predictions. If significant, introduce control of these characteristics.*
- *When comparing CU results by NIR and UHPLC you should use the calculation proposed in the procedure. The results reported in batch analysis section are calculated for 60 tablets using approach different from standard USP calculation.*
- *For tablets outside the target concentration prepared in the lab indicate differences in appearance (shape, size dimensions, indentation) and properties (hardness, (b) (4) from the production samples.*
- *Please note that if the method is used at multiple sites, it should be validated at each site and submitted to the Agency, unless it is demonstrated that the method is transferable.*

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/s/

DANAE D CHRISTODOULOU
08/11/2014



IND 110533

MEETING MINUTES

Janssen Research & Development, L.L.C.
Attention: Sukhdev K. Saran
Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Saran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for canagliflozin and metformin hydrochloride extended release tablets.

We also refer to the telecommunication between representatives of your firm and the FDA on June 25, 2014. The purpose of the meeting was to discuss the proposed content of the New Drug Application (NDA) to be submitted next year.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 25, 2014, 2:00 to 3:30 PM
Meeting Location: Teleconference

Application Number: IND 110533, NDA 205879
Product Name: canagliflozin and metformin hydrochloride extended release tablets
Indication: treatment of type 2 diabetes mellitus
Sponsor/Applicant Name: Janssen Research and Development, L.L.C.

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Elizabeth Chen, Pharm.D.

FDA ATTENDEES
CDER Participants:

Division of Metabolism and Endocrinology Products (DMEP)

Jean-Marc Guettier, M.D., Director
Lisa Yanoff, M.D., Clinical Team Leader
Hyon Kwon, Pharm.D., MPH, Clinical Reviewer
Fred Alavi, Ph.D., Pharmacology/Toxicology Reviewer
Elizabeth Chen, Pharm.D., Regulatory Project Manager
Pamela Lucarelli, Chief, Project Management Staff

Division of Biometrics II

Mark Rothmann, Ph.D., Team Leader
Anna Kettermann, Dipl. Math, MA., Statistical Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Lokesh Jain, Ph.D., Team Leader

SPONSOR ATTENDEES

Biostatistics & Programming

Norman R. Bohidar, Ph.D., Clinical Biostatistics Head, Cardiovascular and Metabolism

Clinical

Gary Meininger, M.D., Franchise Medical Leader, Metabolism
Rose (Rong) Qiu, M.D., Ph.D., Study Physician

Clinical Pharmacology, Translational Medicine, and Pharmacogenomics

Clapton Dias, Ph.D., Scientific Director, Clinical Pharmacology Leader
Kenneth Turner, Ph.D., Clinical Pharmacology Therapeutic Area Head
David Polidori, Ph.D., Head of Clinical and Translational Biomarkers, Cardiovascular and Metabolism

Compound Development Team

Norman Rosenthal, M.D., Vice President, Canagliflozin Compound Development Team Leader
Hamish Ross, Ph.D., Vice President, Clinical Research, Canagliflozin/Metformin FDC
Compound Development Team Leader

Global Dossier Submissions

Lorraine T Petrozziello, Associate Director, Global Dossier Leader

Global Regulatory Affairs

Jacqueline Coelln-Hough, RPh, Sr Director, Global Regulatory Affairs
Brandon Porter, MBA, Associate Director, Regulatory Affairs
Sukhdev Saran, MBA, Director, Regulatory Affairs

Preclinical

Mark Johnson, Ph.D., Director, Preclinical Development

Preclinical

Mark Johnson, Ph.D., Director, Preclinical Development

1.0 BACKGROUND

Canagliflozin is an orally active inhibitor of renal sodium-glucose co-transporter-2 (SGLT2). The New Drug Application (NDA) for canagliflozin tablets was approved on March 29, 2013, for treatment of type 2 diabetes mellitus (T2DM).

The Investigational New Drug (IND) application for fixed-dose combination product of canagliflozin and metformin hydrochloride extended-release tablets was submitted on January 6, 2011. The 30-day review period was waived due to the existence of an active IND for the canagliflozin single agent.

A Pre-NDA meeting with Chemistry, Manufacturing, and Controls (CMC) was requested on September 18, 2013, and granted on September 30, 2013, with written responses only. These responses issued on November 25, 2013. Therefore, CMC questions were not addressed at this meeting.

The purpose of this meeting is to discuss the content of the NDA for canagliflozin and metformin hydrochloride extended-release tablets, to be submitted early in 2015. Janssen Research & Development LLC has right-of-reference to the Glumetza (metformin hydrochloride extended-release tablets) NDA, and plans to submit a 505(b)(1), relying on data previously submitted in the application for both the canagliflozin single agent and canagliflozin and metformin hydrochloride (immediate release) fixed-dose combination tablets. There are no new pivotal clinical studies to be reviewed in this NDA.

For convenience in these meeting minutes, the product is referred to as CANA/MET XR FDC.

2.0 DISCUSSION

2.1. Non-Clinical

Question 1: *JRD intends to cross-refer to the nonclinical pharmacology, PK, and toxicology study reports submitted to the canagliflozin NDA (204042) as support for the CANA/MET XR FDC. These include reports for the 3-month rat toxicity study (TOX9667) and the Segment II rat study (TOX9590) with canagliflozin (at up to 100 and 60 mg/kg/day, respectively) in combination with metformin (300 mg/kg/day). As the Agency requested resubmission of these 2 canagliflozin and metformin combination studies for the CANA/MET IR FDC NDA, these 2 studies will also be resubmitted for the CANA/MET XR FDC. Does the Agency agree that, in the absence of new impurities from ongoing stability studies, these studies provide sufficient preclinical data for the CANA/MET XR FDC?*

FDA Response to Question 1: **Unless new impurities are identified in the ongoing stability studies, the referenced nonclinical studies appear to support the CANA/MET XR FDC.**

Discussion: **No discussion occurred.**

2.2. Clinical Pharmacology

Question 2: *As agreed in the 30 August 2010 FDC EOP2 meeting, JRD conducted a drug-drug interaction (DDI) study with 300 mg canagliflozin and 2,000 mg metformin IR. This study (DIA1028) was submitted with the canagliflozin NDA (204042). JRD intends to cross-refer to the canagliflozin NDA (204042) for the DIA1028 study in this NDA filing. Does the Agency agree?*

FDA Response to Question 2: **Yes, we agree. In addition, as discussed in the End-of – Phase 2 (EOP2) meeting, a study on the effects of alcohol with the to-be-marketed CANA/MET XR FDC tablet is needed due to concerns related to “dose-dumping.” An *in vitro* study will be sufficient if the results are negative, however, if there are any positive results, an *in vivo* trial will be required.**

Discussion: The sponsor clarified that dose-dumping study results have been submitted for review by the Agency in a separate Type C meeting. The Agency acknowledged and agreed that it will be reviewed under that meeting.

2.3. Clinical

Question 3: *To support usage of the CANA/MET XR FDC formulation in the pediatric/adolescent population, the sponsor proposes to conduct a swallowability study using placebo tablets with the same dimensions and shape as the current to-be-marketed CANA/MET XR FDC tablets in T2DM subjects to determine whether a specific pediatric formulation will need to be developed. If the current CANA/MET XR FDC tablets are deemed acceptable in terms of swallowability, the sponsor then proposes to support usage of the CANA/MET XR FDC formulation in the pediatric/adolescent population using the available relevant data from the adult clinical program for the canagliflozin NDA (204042), the Glumetza NDA (21748) (for which the sponsor has right of reference), the adult BE studies for the proposed commercial formulation in the CANA/MET XR FDC NDA (205879) (DIA1041, DIA1044, DIA1062, and DIA1063), and the planned pediatric studies for canagliflozin as agreed with the Agency (canagliflozin NDA [204042] – PMR 2027-1 and PMR 2027-2) to support the extrapolation of efficacy to the pediatric population and provide relevant safety information in the pediatric population. Does the Agency agree?*

FDA Response to Question 3: In order to assess your proposal for a swallowability study, you should provide the exact dimensions for the to-be-marketed CANA/MET XR FDC tablet.

Your overall approach to satisfy the Pediatric Research Equity Act (PREA) requirements appears reasonable. See also our response to question 4.

Discussion: See question 4.

Question 4: *In this pre-NDA meeting, JRD is seeking preliminary feedback from the Agency regarding the pediatric proposal for the CANA/MET XR FDC prior to the submission of the initial Pediatric Study Plan (PSP). In accordance with Title V, section 506 of the Food and Drug Administration Safety Innovation Act and the FDA Draft Guidance for Industry, “Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans” (July 2013), JRD respectfully requests to submit the initial PSP no more than 60 days after the Pre-NDA meeting to incorporate the Agency’s feedback. Does the Agency agree with this proposal?*

FDA Response to Question 4: Sponsors must submit the initial PSP no later than 60 days after the date of the EOP2 meeting. In the absence of an EOP2 meeting, sponsors should submit the initial PSP no later than 210 days before a marketing application is submitted. For additional information, refer to Section 3.0 PREA Requirements, below.

Discussion: The sponsor agreed to email the exact tablet dimensions to the Agency after the meeting for assessment of a swallowability study. The Agency also reiterated that the sponsor should submit the initial PSP per the standard timelines.

2.4. Regulatory

Question 5: *The efficacy, safety, and posology of the CANA/MET XR FDC is supported by the following studies:*

- *the same Phase 3 studies that supported efficacy in the canagliflozin NDA (204042) and the CANA/MET IR FDC NDA (204353) (DIA3002, DIA3006, DIA3008, DIA3009, DIA3010, DIA3012, and DIA3015),*
- *the same 9 Phase 3 studies that supported safety in the canagliflozin NDA (204042) and the CANA/MET IR FDC NDA (204353),*
- *studies in the Glumetza NDA (21748) that show Glumetza is equivalent to metformin IR. The above-mentioned canagliflozin Phase 3 studies utilized both metformin IR and XR (except DIA3006 which used only metformin IR). JRD intends to rely on the studies in the Glumetza NDA (21748) to demonstrate that Glumetza has comparable efficacy and safety to the metformin IR formulation,*
- *four Phase 1 studies (1 for each strength of the CANA/MET XR FDC; DIA1041, DIA1044, DIA1062, and DIA1063) demonstrating the bioequivalence of the to-be-marketed CANA/MET XR FDC to the individual components of canagliflozin and Glumetza,*
- *a 7-day multidose PK study of the 150/1,000 mg CANA/MET XR FDC tablet evaluating the PK of multiple doses of the CANA/MET XR FDC tablets (DIA1042), and*
- *a food effect study evaluating the effect of food on canagliflozin bioavailability following single-dose administration of the 150/1,000 mg CANA/MET XR FDC tablet (DIA1064).*

Does the Agency agree that the above studies provide sufficient support for:

- 1) the efficacy evaluation of the CANA/MET XR FDC?*
- 2) the safety evaluation of the CANA/MET XR FDC?*
- 3) the recommended posology of taking 2 tablets once-daily*

(b) (4)

FDA Response to Question 5: The above studies appear to provide sufficient information to evaluate the efficacy and safety of the CANA/MET XR FDC, although efficacy and safety conclusions will be a review issue.

(b) (4)

Discussion: During the meeting, the sponsor presented slides on the renal threshold for glucose and urinary glucose excretion (UGE) to address the Agency's safety concerns about administering canagliflozin (b) (4). The Agency indicated that the adverse events (b) (4) are not necessarily related to UGE, and have concerns about the potential for increased risk of volume-related adverse events (b) (4) in vulnerable patient populations with (b) (4) dosing of canagliflozin. The Agency stated that the currently available data do not support dosing of CANA/MET XR FDC (b) (4).

The Agency agreed with the sponsor that the current proposed package for Glumetza provides sufficient data to support morning dosing of the CANA/MET XR FDC product.

Question 6: JRD intends to include 2 data sets with this CANA/MET XR FDC NDA (DS1 and DS1-M) (refer to Table 11) to support the safety and tolerability of the CANA/MET XR FDC through 26 weeks.

In addition to the 2 data sets (DS1 and DS1-M) and consistent with the approach of the safety update in the CANA/MET IR FDC NDA resubmission, JRD intends to provide the following safety information for the CANA/MET XR FDC NDA:

- A. A summary of safety data through 31 December 2012 based on the Broad Dataset (also referred to as DS3) (Table 10). Note that this was included in JRD's most recent submission of integrated safety data (4-month safety update [4MSU] for the CANA/MET IR FDC NDA).
- B. For ongoing studies as of the proposed data cutoff of 30 September 2014 (eg, DNE3001, DIA3008, DIA3011, DIA4002, DIA4003, and DIA4004), to maintain data integrity, JRD proposes not to unblind subject-level data from these studies for the Integrated Summary of Safety (ISS) (as they will still be ongoing and blinded at that time). The incremental blinded output of the number and proportion of subjects randomized with deaths, serious adverse events (SAEs), or drug discontinuations due to an adverse event (AE), along with the corresponding listing of such subjects, will be provided (from 01 January 2013 through 30 September 2014).
- C. For studies to be initiated immediately prior to the proposed data cut-off date of 30 September 2014 (DIA2004 [Type 1 Diabetes Proof of Concept Study] and OBE2002 [Obesity Proof of Concept Study]), JRD proposes to provide blinded outputs of the number and proportion of subjects randomized with deaths, SAEs, or drug discontinuations due to an adverse event (AE) along with the corresponding listing of these subjects in the XR FDC 4MSU.
- D. The canagliflozin annual enhanced pharmacovigilance report (reporting period 29 March 2013 through 31 March 2014) supporting canagliflozin PMR 2027-3.

Does the Agency agree that the proposed data sets plus the above-listed safety information, plus the annual enhanced pharmacovigilance report are sufficient for evaluation of the safety of the CANA/MET XR FDC?

FDA Response to Question 6: Yes, the above safety information appears to be sufficient for evaluation of the safety of the CANA/MET XR FDC. We may request unblinded data and/or narratives if safety concerns arise during our review of these data.

Discussion: No discussion occurred.

Question 7: *As was done in the CANA/MET IR FDC NDA (204353), JRD intends to cross-refer to the data in the canagliflozin NDA (204042) to demonstrate the efficacy of the co-administration of canagliflozin and metformin. JRD intends to provide a summary of the Phase 1 studies (without pooling the new Phase 1 data) in the integrated summary of efficacy (ISE) in the CANA/MET XR FDC NDA (205879). Because no additional studies with an efficacy evaluation of concurrent dosing of both canagliflozin and metformin have been reported since the canagliflozin NDA (204042) was filed, JRD believes that the data in that NDA is still the most representative efficacy dataset for this CANA/MET XR FDC NDA (205879). Accordingly, JRD does not intend to provide any new data pooling for efficacy evaluation of the CANA/MET XR FDC program. Does the Agency agree that this approach is appropriate for evaluation of the efficacy of the CANA/MET XR FDC?*

FDA Response to Question 7: We agree with cross-referencing and not submitting any new data pooling for efficacy evaluation of the CANA/MET XR FDC program. To facilitate review, please include electronic hyperlinks to cross-referenced data. You should include summaries and discussions relevant to the efficacy of the CANA/MET XR FDC.

Discussion: See question 14.

Question 8: *As the Glumetza NDA (21748) demonstrates that the XR and IR metformin have comparable safety and efficacy, JRD does not intend to cross-refer to the Glucophage (metformin IR) NDA (20357). Does the Agency agree with this proposal?*

FDA Response to Question 8: Yes, your proposal is acceptable.

Discussion: No discussion occurred.

Question 9: *JRD intends to submit the CANA/MET XR FDC NDA (205879) under Section 505(b)(1) the Federal Food, Drug, and Cosmetic Act because JRD holds the canagliflozin NDA (204042) and has a right of reference to the Glumetza NDA (21748). Does the Agency agree:*

- 1) *that this NDA should be submitted under Section 505(b)(1),*
- 2) *that cross-referencing the nonclinical and clinical information from the Glumetza NDA (21748) is sufficient, and*

3) *that submitting published literature on metformin is not necessary?*

FDA Response to Question 9: Yes, your proposal is acceptable, provided you have obtained right of reference to the Glumetza NDA.

Discussion: No discussion occurred.

Question 10: *JRD intends to submit a literature review of publications regarding canagliflozin, excluding any publications produced by the sponsor that contain clinical data from studies that have already been submitted to the Agency. Does the Agency agree with this proposal?*

FDA Response to Question 10: We agree with your proposal.

Discussion: No discussion occurred.

Question 11: *JRD proposes referring to the published literature in the canagliflozin NDA (204042) and only submitting copies of new publications cited in Module 2 summaries of the CANA/MET XR FDC NDA (205879). Does the Agency agree with this proposal?*

FDA Response to Question 11: We agree with your proposal.

Discussion: No discussion occurred.

Question 12: *JRD intends to submit financial disclosure information only for the clinical investigators involved in the new clinical studies (DIA1041, DIA1044, DIA1062, DIA1063, DIA1042, and DIA1064; see Table 4 for information about these studies) to be included in the CANA/MET XR FDC NDA (205879). Does the Agency agree with this approach?*

FDA Response to Question 12: We agree with this approach. Financial disclosure information is required only for covered clinical studies not previously submitted.

Discussion: No discussion occurred.

Question 13: *JRD intends to include copies of available Periodic Adverse Drug Experience Reports (PADER) and Periodic Safety Update Reports (PSUR) from the overall canagliflozin program in Module 5.3.6, Reports of Post-Marketing Experience. Does the Agency agree that this will satisfy the requirements for this Module?*

FDA Response to Question 13: We agree that the submission of PADER and PSUR will satisfy requirements for Module 5.3.6.

Discussion: No discussion occurred.

Question 14: *With the exception of Phase 1 PK, BE, and food effect studies, the CANA/MET XR FDC NDA (205879) will rely primarily on the safety and efficacy data in the*

canagliflozin NDA (204042) and the Glumetza NDA (21748). Accordingly, JRD intends to cross-refer to those NDAs as follows:

- *Non-clinical Studies: Except for the 3-month toxicity rat study (TOX9667) and the Segment II rat study (TOX9590) mentioned in Question 1 above, JRD intends to cross-refer to the non-clinical study reports in the canagliflozin NDA (204042) and the Glumetza NDA (21748) and not include any copies in the CANA/MET XR FDC NDA (205879). Does the Agency agree with this non-clinical study cross-reference proposal?*
- *Clinical Studies: JRD intends to cross-refer to the clinical study reports in the canagliflozin NDA (204042) and the Glumetza NDA (21748) and only include study reports specific to the CANA/MET XR FDC (eg, BE, PK, DDI, and food effect studies) in the CANA/MET XR FDC NDA (205879). Does the Agency agree with this clinical study cross-reference proposal?*
- *Module 2 and Module 5 Summaries: As was done for the CANA/MET IR FDC NDA (204353), JRD intends to utilize an “addendum” strategy for updating the canagliflozin Module 2 summaries and the Module 5 ISS and ISE with the new XR-specific information where applicable. These CANA/MET XR FDC addenda summaries will cross refer via electronic hyperlinks to the canagliflozin NDA (204042) canagliflozin summaries. To facilitate the electronic hyperlinking, the canagliflozin summaries from canagliflozin NDA (204042) will also be included in this CANA/MET XR FDC NDA (205879). To optimize readability and flow, selected canagliflozin Module 2 summaries may be fully integrated with the new CANA/MET XR FDC data (and where appropriate with new canagliflozin data as well) instead of utilizing the addendum strategy. The approach taken for each summary will be explained in the NDA reviewer’s guide.*
 - *Does the Agency agree with the Module 2 FDC addenda cross-referencing strategy?*
 - *Does the Agency agree that the cross-referring strategy for the Module 5 ISE is acceptable and fulfills the requirements for an ISE under 21 CFR 314.50(d)(5)(v) for the CANA/MET XR FDC NDA (205879)?*
 - *Does the Agency agree that the cross-referring strategy for the Module 5 ISS is acceptable and fulfills the requirements for an ISS under 21 CFR 314.50(d)(5)(vi)(a) for the CANA/MET XR FDC NDA (205879)?*

FDA Response to Question 14: Yes, we agree your cross-reference proposal for clinical studies, Module 2 FDC addenda, and Module 5 ISE and ISS. To facilitate review, please include electronic hyperlinks to cross-referenced data.

Discussion: The Agency asked whether any new or additional safety data will be available in the CANA/MET XR FDC NDA from ongoing studies, and the sponsor responded that no new unblinded data will be available since the CANA/MET immediate release FDC NDA resubmission in February 2014. The sponsor also stated that hyperlinking from one to another NDA is problematic, and will copy the single agent canagliflozin summary documents into the CANA/MET XR FDC NDA and provide hyperlinks only to those summaries. No CSRs, data sets, or any other items from the canagliflozin single agent NDA will be included in the CANA/MET

XR NDA, and will not be hyperlinked if referenced. The Agency agreed with this proposal.

Question 15: *Similar to the proposal for the ISS in the CANA/MET XR FDC NDA (205879) submission, JRD proposes the following contents for the 4MSU of the CANA/MET XR FDC NDA (205879):*

- *For ongoing studies (e.g., DIA3008, DIA4002, DIA4003, DIA4004, and DNE3001) and studies initiated immediately prior to the CANA/MET XR FDC NDA (205879) cut-off date (DIA2004 and OBE2002): to maintain data integrity, JRD proposes not to unblind subject-level data from these studies (as they should still be ongoing and blinded as of the proposed 31 January 2015 data cutoff). The incremental blinded output of the number and proportion of subjects randomized with deaths, SAEs, or drug discontinuations due to an AE, along with the corresponding listing of these subjects will be provided from the CANA/MET XR FDC NDA (205879) cut-off date of 30 September 2014 through 31 January 2015.*
- *For DIA3011 which should be completed by the CANA/MET XR FDC 4MSU data cut-off date, JRD proposes to provide the clinical study report (CSR).*
- *The canagliflozin annual enhanced pharmacovigilance report (reporting period 29 March 2014 through 31 March 2015) supporting canagliflozin PMR 2027-3. Since this 4MSU is expected to be due at approximately the same time as the enhanced pharmacovigilance report (due 30 May 2015), JRD respectfully requests a 2-week grace period/extension of the 4MSU due date to accommodate the inclusion of this report in the 4MSU.*
 - 1) *Does the Agency agree that the inclusion of these items will be sufficient to satisfy the requirements of the 4MSU?*
 - 2) *Does the Agency agree with the requested 2-week extension on the 4MSU due date if needed to include the enhanced pharmacovigilance report?*

FDA Response to Question 15: We agree with your proposal.

Discussion: No discussion occurred.

Question 16: *JRD intends to file a supplemental NDA (sNDA) to include data from 1 additional Phase 3 study (DIA3011) to support a first-line therapy indication for the CANA/MET XR FDC tablets. JRD proposes to include the following items in that sNDA:*

- *Module 1: cover letter, forms, user fee documents, debarment, proposed labeling (container labels, United States Package Insert [USPI] annotated/marked/clean versions, Structured Product Labeling [SPL]), etc.*
- *Module 2: clinical overview including the new DIA3011 clinical study data and no other summaries.*
- *Module 3: no new Module 3 information as the proposed change to first-line therapy does not involve any CMC changes.*
- *Module 4: no new Module 4 information as the proposed change to first line therapy does not involve any nonclinical changes.*

- *Module 5:*
 - *Updated list of studies (to include DIA3011)*
 - *DIA3011 CSR and associated documents (case report forms [CRFs], data sets, financial disclosures, etc.)*
 - *No revised ISS or ISE.*
 - *Literature references as needed.*

Does the Agency agree that the inclusion of these items will be sufficient to support the evaluation of the proposed first line therapy indication?

FDA Response to Question 16: We are unable to provide agreement at this time, as we have not reviewed your study protocol for DIA3011 and have not determined if this study will be sufficient to support the first line therapy indication. Please see also our response to question 5. Even if study DIA3011 includes dosing of CANA/MET XR FDC

(b) (4)

This would be a review issue.

Discussion: The Agency restated that it is unable to provide agreement at this time because this topic is not the focus of the meeting and not relevant to the initial CANA/MET XR FDC NDA. The Agency advised the sponsor to request a separate pre-sNDA meeting to discuss this topic. The sponsor stated that the protocol for DIA3011 was submitted to the IND and that they had received Agency's comments regarding the protocol. The Agency stated that these comments were intended to provide assistance in designing an adequate protocol and should not be taken as 'agreement' regarding approvability of a supplemental NDA to support a first-line therapy indication for the CANA/MET XR FDC tablets.

Question 17: *To maximize consistency between the two fixed dose combination product labels, JRD intends to reference the CANA/MET XR FDC USPI to the CANA/MET IR FDC USPI (NDA 204353; currently under review with a 10 August 2014 action date) to support text related to canagliflozin and metformin that is common between the two products. In addition, to support text related specifically to extended release metformin in the CANA/MET XR FDC USPI, JRD plans to include annotations to the Glumetza USPI (NDA 21748). JRD also intends to include a cross-reference to both NDAs (204353 and 21748) in the CANA/MET XR FDC NDA Module 1.4.4 Letter of Cross Reference to Other Applications. Does the Agency agree with this annotation and cross-reference approach for the CANA/MET XR FDC USPI?*

FDA Response to Question 17: We agree with your proposal.

Discussion: No discussion occurred.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

5.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

6.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit initial pediatric study plan (iPSP)	Sponsor	June 27, 2014 (completed)
Provide dimensions of tablets by e-mail	Sponsor	June 25, 2014 (completed)

7.0 ATTACHMENTS AND HANDOUTS

Attached please see slides for Question 5.

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JEAN-MARC P GUETTIER
07/25/2014

From: [Van der Waag, Julie](#)
To: [Porter, Brandon \[JRDUS\] \(BPorter3@its.jnj.com\)](#)
Cc: [Adeolu, Abolade](#); [Chen, Elizabeth](#)
Subject: FW: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question
Date: Wednesday, January 29, 2014 7:07:20 AM
Attachments: [Janssen - Glumetza Strengths in XR FDC BE Studies - 28Jan2014.pdf](#)
[EoP2 Mtg - FDC - FDA Minutes - 30Sep2010.pdf](#)
[emfinfo.txt](#)

Good Morning Brandon,

The project manager who is assigned to the canagliflozin and metformin XR IND is Elizabeth Chen. I have included Elizabeth on this email.

When do you anticipate submitting this NDA?

Thanks,
Julie

Please note new name and email address
Julie Van der Waag (formerly Marchick)
Chief, Regulatory Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.vanderwaag@fda.hhs.gov

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Tuesday, January 28, 2014 6:01 PM
To: Adeolu, Abolade
Cc: Van der Waag, Julie
Subject: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Hi Bola,
I could not confirm in my records if you will be handling the CanaMet XR FDC program (IND 110,533 / NDA 205,879).

If you are, great! I have included a clarifying question in the attached document regarding the use of multiple 500 mg Glumetza reference tablets in our XR BE studies. It is a fairly straightforward follow up question to the 2010 End of Phase 2 meeting communications in which this issue was mentioned in our briefing document, but not specifically answered in the Agency response. I have also enclosed the FDA minutes of that meeting for reference in case they are helpful.

If you are not handling this product, perhaps I can ask Ms. Marchick the best way to handle this request.

Many thanks to you both for your help.

Best,

Brandon

From: [Porter, Brandon \[JRDUS\]](#)
To: [Chen, Elizabeth](#)
Cc: [Saran, Sukhdev \[JRDUS\]](#)
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question
Date: Tuesday, February 18, 2014 11:17:56 AM
Attachments: [emfalert.txt](#)

Thank you Elizabeth!
Have a great day.
Brandon

From: Chen, Elizabeth [mailto:Elizabeth.Chen@fda.hhs.gov]
Sent: Tuesday, February 18, 2014 7:39 AM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Hi Brandon,

Thanks for following up. I hope this is not too late, but the reviewers have stated that they have no issue with use of multiples of Glumetza 500 mg as reference in these studies.

Regards,
Elizabeth

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Friday, February 14, 2014 12:00 PM
To: Chen, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Hi Elizabeth,
Just wanted to check in to see if you have any update on this item.
Many thanks and Happy Valentine's Day!
Best,
Brandon

From: Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]
Sent: Friday, February 07, 2014 1:07 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Dear Brandon,

Unfortunately, I can't guarantee a response by next Wednesday, but the assigned reviewers (one of whom is not as familiar with the program) are aware that you need a response from them as soon as possible. Feel free to follow up early next week, and I will let you know the status.

Thanks,

Elizabeth

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Thursday, February 06, 2014 4:43 PM
To: Chen, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Thank you Elizabeth.

Would it be possible to request a response by next Wednesday, February 12th? These protocols are already written, have been submitted to the IND, and are scheduled to start this month. This question was to confirm that we had a proper understanding of the Agency's position before we start these trials. Many thanks for your help.
Best,
Brandon

From: Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]
Sent: Thursday, February 06, 2014 1:13 PM
To: Porter, Brandon [JRDUS]
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Hi Brandon,

While I've forwarded your questions to the reviewers, I don't yet have any estimate on when you might expect a response. I will keep you posted and forward you information as soon as I receive it.

Thanks,
Elizabeth

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Wednesday, February 05, 2014 5:04 PM
To: Chen, Elizabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Hi Elizabeth,
I am writing to follow up on the BE study design question I submitted below. Do you have an estimate on when we could expect to receive a response on this?
Many thanks.
Best,
Brandon

From: Porter, Brandon [JRDUS]
Sent: Wednesday, January 29, 2014 5:24 AM
To: 'Van der Waag, Julie'
Cc: 'Abolade.Adeolu@fda.hhs.gov'; 'Elizabeth.Chen@fda.hhs.gov'
Subject: RE: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Hi Julie,

I apologize for not using your new last name; I created a new contact card for you a while back and failed to delete my old contact card. ☺

Thank you for letting me know that Elizabeth is the project manager for this program. The current estimated submission date for this NDA is January 2015, however, we are requesting clarity now on the BE study design as these trials need to start very soon if we are to make the January NDA submission date.

Many thanks for your help.

Best Regards,
Brandon

From: Van der Waag, Julie [<mailto:Julie.VanderWaag@fda.hhs.gov>]
Sent: Wednesday, January 29, 2014 7:07 AM
To: Porter, Brandon [JRDUS]
Cc: Adeolu, Abolade; Chen, Elizabeth
Subject: FW: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Good Morning Brandon,

The project manager who is assigned to the canagliflozin and metformin XR IND is Elizabeth Chen. I have included Elizabeth on this email.

When do you anticipate submitting this NDA?

Thanks,
Julie

Please note new name and email address
Julie Van der Waag (formerly Marchick)
Chief, Regulatory Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.vanderwaag@fda.hhs.gov

From: Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]
Sent: Tuesday, January 28, 2014 6:01 PM
To: Adeolu, Abolade
Cc: Van der Waag, Julie
Subject: CanaMet XR FDC (IND 110,533; NDA 205,879) / BE Study Question

Hi Bola,

I could not confirm in my records if you will be handling the CanaMet XR FDC program (IND 110,533 / NDA 205,879).

If you are, great! I have included a clarifying question in the attached document regarding the use of multiple 500 mg Glumetza reference tablets in our XR BE studies. It is a fairly straightforward follow up question to the 2010 End of Phase 2 meeting communications in which this issue was mentioned in our briefing document, but not specifically answered in the Agency response. I have also enclosed the FDA minutes of that meeting for reference in case they are helpful.

If you are not handling this product, perhaps I can ask Ms. Marchick the best way to handle this request.

Many thanks to you both for your help.

Best,

Brandon

From: [Vaidyanathan, Jayabharathi](#)
To: [Chen, Elizabeth](#); [Kwon, Hyon](#)
Cc: [Jain, Lokesh](#)
Subject: RE: IND 110533/NDA 205879 - cana/met XR/Janssen - BE Study Question
Date: Tuesday, February 18, 2014 10:33:43 AM

Hi Liz,

We reviewed the sponsor's request.

Please let sponsor know that we agree with the use of multiples of Glumetza 500 mg strength as reference in their studies.

Thanks,
Jaya

From: Chen, Elizabeth
Sent: Friday, February 07, 2014 9:34 AM
To: Kwon, Hyon; Vaidyanathan, Jayabharathi
Subject: IND 110533/NDA 205879 - cana/met XR/Janssen - BE Study Question

Dear KC and Jaya,

I hope I'm sending this to the right place. Janssen has submitted a question by e-mail related to their planned BE study (use of multiple 500 mg Glumetza reference tablets) for the planned cana/met XR NDA. I've attached the EoP2 meeting minutes which contain the original discussion, as well as their inquiry.

The sponsor has requested a response by Wednesday, February 12 (next week). Please let me know if this is feasible.

Thanks,
Liz

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

/s/

ELIZABETH R CHEN
02/19/2014



IND 110533

**MEETING REQUEST-
WRITTEN RESPONSES**

Janssen Research & Development L.L.C
Attention: Sukhdev K Saran, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Saran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-28431754 (canagliflozin).

We also refer to your September 18, 2013, correspondence requesting a meeting to discuss proposed content of the CMC section of the New Drug Application (NDA 205879) to be submitted in 4Q/2014 by JRD.

Further reference is made to our Meeting Granted letter dated September 30, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 18, 2013 background package.

If you have any questions, call me at (240) 402-3722.

Sincerely,

{See appended electronic signature page}

Danae Christodoulou, Ph.D.
Branch Chief (Acting)
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA CMC Meeting

Application Number: 110533
Product Name: JNJ-28431754 (canagliflozin)/ JNJ-1158196 (metformin hydrochloride) XR FDC
Indication: Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Janssen Research & Development, L.L.C

1.0 BACKGROUND

Janssen Research & Development (JRD) has developed canagliflozin (Cana), a sodium glucose co-transporter 2 (SGLT2) inhibitor, for the treatment of type 2 diabetes mellitus. The primary objective of this pre-NDA CMC meeting is to obtain agreement with the Agency regarding the proposed content of the CMC section of the New Drug Application (NDA 205879) to be submitted in 4Q/2014 by JRD. Specific questions to be discussed at this meeting will relate exclusively to the CANA/MET XR FDC NDA submission and will include questions only in the CMC functional discipline. JRD intends to request a subsequent pre-NDA meeting to discuss non-CMC related issues sometime in the first half of 2014.

2. QUESTIONS AND RESPONSES

2.1. Category/Discipline A

Question 1: Does the Agency agree with the cross-references to the approved INVOKANA® (canagliflozin) tablet NDA 204042 for all canagliflozin drug substance information, and to the (b) (4) DMF for all metformin hydrochloride drug substance information?

FDA Response to Question 1: *We agree with your proposal to cross-reference NDA 204042 for all canagliflozin drug substance information and to cross-reference the (b) (4) DMF for the metformin hydrochloride drug substance information. In your NDA submission, include drug substance(s) acceptance specifications and supporting Certificates of Analyses for your NDA drug substance(s) batches.*

Question 2: The Sponsor plans to submit one executed batch record from a single representative batch of each tablet strength (50/500, 150/500, 50/1000 and 150/1000-mg) of Cana/Met XR FDC tablets, manufactured to support the primary stability studies.

Does the Agency agree with this approach?

FDA Response to Question 2: *You may submit one executed batch record from a single representative batch of each tablet strength if the batches for each tablet strength used for the Phase 3 clinical trials were made in the same way (method, equipment, site and scale) as the batches manufactured to support the primary stability studies. If this is not the case, you should also provide the batch records from the production of the largest scale batch of each strength used for these Phase 3 trials.*

Question 3: On 30 August 2010, a type B, End-of-Phase 2 (EOP2) meeting was held between FDA and JRD representatives in which the development of the Cana/Met XR FDC tablets was discussed. As requested by the Agency, the Sponsor submitted dissolution method development data to the Canagliflozin/Metformin IND 110,533, on 21 June, 2013 (b) (4)

Does the Agency agree with the proposed dissolution methods?

FDA Response to Question 3: *The proposed dissolution methods appear reasonable; however, you have not proposed Dissolution Acceptance Criteria yet.*

For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

- a) *The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).*
- b) *Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
- c) *A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least (b) (4) % of drug has release. If the maximum amount release is less than (b) (4) %, the last time point should be the time when the plateau of the release profile has been reached.*

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

In addition, we are concerned that your modified release (MR) product may release its entire contents (“dose dumping”) when used with alcohol, thereby leading to safety concerns. Therefore, we recommend that you conduct a drug-alcohol interaction study with your MR product. You should conduct in vitro drug release testing initially using the highest strength and you may have to follow-up with an in vivo study, depending on the result of the in vitro testing. You should discuss the result of your in vitro study with the Agency prior to the NDA submission.

- a. *The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.*
- b. *Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.*
- c. *Report f_2 values to assess the similarity (or lack thereof) in the dissolution profiles.*
 - *Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.*
 - *The report should include the complete data (i.e., individual, mean, SD, comparison plots, f_2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.*

Question 4: The metformin HCl XR layer of the Cana/Met XR FDC tablets has been developed in alignment with the commercial Glumetza® tablets, 500 mg. The approved timepoints for the Glumetza® release rate are 120, 240 and 720 minutes.

Does the Agency agree that the timepoints 120, 240 and 720 minutes, as applicable to the commercial Glumetza® 500 mg tablets, can also be applied for metformin hydrochloride release for the Cana/Met XR FDC tablets?

FDA Response to Question 4: Yes, the use of the established sampling time point for the extended release portion of the product is acceptable.

Question 5: Does the Agency agree with the Sponsor’s proposal to demonstrate comparability between the tablets manufactured with the metformin hydrochloride granulates manufactured at the Janssen-Ortho, LLC site (b) (4)? Additionally, if similarity of the tablet in-vitro dissolution profiles is demonstrated, does the Agency agree that no further BE studies on the finished drug product are needed to support (b) (4) as alternative granulation site for the metformin HCl granulate?

FDA Response to Question 5: No, we do not agree. As your proposed product is a combination of immediate release (IR) and extended release (ER) components, you need to fulfill the following two requirements from biopharmaceutics perspective as per SUPAC-ER guidance for solid oral products in addition to required CMC requirements:

Dissolution documentation: A multipoint dissolution profile should be obtained using approved test conditions for the final drug products manufactured with metformin hydrochloride granulates manufactured at the original and proposed alternate sites. Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either (b) (4) % of the drug from the drug product is released or an asymptote is reached. Similarities in the dissolution profiles need to be established using f2 matrix.

Bioequivalence documentation: A single-dose bioequivalence study to establish bioequivalence between the final drug products manufactured with metformin hydrochloride granulates manufactured at the original and proposed alternate sites. The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (IVIVC).

Additional information: *You stated your intention to place one batch of each strength of Cana/Met XR FDC tablets manufactured with (b) (4) Metformin HCl granulate on stability, to compare their stability behavior with tablets manufactured with Janssen-Ortho, LLC Metformin HCl granulate, for which 3 batches per tablet strength will be placed on stability. At the time of submission, at least 3 months accelerated stability data of Cana/Met XR FDC tablets manufactured with (b) (4) Metformin HCl granulate will be available and included in the NDA. However, for a bridging study such as this, you should provide, at the time of your NDA submission, 6 months of accelerated stability data plus the (b) (4) results from the 6 month time points from long term stability studies.*

(b) (4)

(b) (4)



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/s/

DANAE D CHRISTODOULOU
11/25/2013



IND 76479

MEETING MINUTES

Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Sukhdev K. Saran
Associate Director, Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Saran:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for canagliflozin.

We also refer to the teleconference between representatives of your firm and the FDA on August 30, 2010. The purpose of the meeting was to discuss a canagliflozin plus immediate or extended-release metformin fixed-dose combination drug product.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: meeting minutes
alcohol/dose dumping advice

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: August 30, 2010; 9:00 A.M.
Meeting Location: teleconference

Application Number: IND 76479
Product Name: canagliflozin (+metformin)
Indication: treatment of type 2 diabetes
Sponsor/Applicant Name: Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

Meeting Chair: Ilan Irony, M.D.
Meeting Recorder: Patricia Madara, M.S.

FDA Attendees

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D. Director
Ilan Irony, M.D. Diabetes Team Leader
Patricia Madara, M.S. Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Sally Choe, Ph.D. Clinical Pharmacology Team Leader

Office of New Drug Quality Assessment; Biopharmaceutics

Angelica Dorantes, Ph.D. Biopharmaceutics Review Lead

Office of New Drug Quality Assessment; Division of Pre-Marketing Assessment I

Suong Tran, Ph.D. Team Lead, Branch 2

Johnson & Johnson Attendees

Yinka Williams, Ph.D. Director, CMC Leader
Peter Pruuost, M.S. Research Fellow, Drug Product Development
Lisa Lumia, Ph.D. Director, CMC Regulatory Affairs
Kirk Ways, M.D., Ph.D. Compound Development Team Leader
Peter Stein, M.D. Head of Development, Metabolism
Gary Meininger, M.D. Franchise Medical Leader, Metabolism
Rose (Rong) Qiu, M.D., Ph.D. Study Physician
Mark Johnson, Ph.D. Director, Preclinical Development
Kenneth Turner, Ph.D. Clinical Pharmacology Therapeutic Area Head
Damayanthi Devineni, Ph.D. Director, Clinical Pharmacology Leader

Surya Mohanty, Ph.D.	Clinical Biostatistics Head
Gordon Law, Ph.D.	Director, Statistical Leader
Jacqueline Coelln-Hough, R.Ph.	Director, Global Regulatory Affairs
Sukhdev Saran, M.B.A.	Associate Director, Regulatory Affairs
Carmen Leung, R.Ph.	Manager, Regulatory Affairs
Lindsay Cobbs, R.Ph.	Associate Director, Regulatory Affairs (FDA Liaison)
Jeffy John	Associate Regulatory Affairs
Christopher Curtain	Senior Scientist, Clinical Pharmacology
Lisa Licata	Associate Director Regulatory Program Manager
Charles Zezza, Ph.D., M.B.A.	Title: Director, Regulatory Affairs

Background

Johnson & Johnson Pharmaceuticals (J&J) is developing canagliflozin (Cana), a sodium glucose co-transporter 2 (SGLT2) inhibitor, for the treatment of type 2 diabetes mellitus. An End-of-Phase 2 meeting for canagliflozin monotherapy was held on April 28, 2009.

The sponsor is also studying canagliflozin use in combination with immediate release (IR) and extended release (XR) metformin (Met). They plan to develop canagliflozin/metformin extended release fixed-dose combination (FDC) tablets and canagliflozin/metformin immediate release FDC tablets in four strengths:

Cana /Met IR FDC (bid dosing with meals)	Cana /Met XR FDC (qd dosing (b) (4))
1 tablet 50 mg/500 mg bid	2 tablets 50 mg/500 mg qd
1 tablet 50 mg/1000 mg bid	2 tablets 50 mg/1000 mg qd
1 tablet 150 mg/500 mg bid	2 tablets 150 mg/500 mg qd
1 tablet 150 mg/1000 mg bid	2 tablets 150 mg/1000 mg qd

On June 2, 2010, J&J submitted a meeting request for a type B, End-of-Phase 2 meeting for the fixed-dose combination drug products. The purpose of the meeting was to obtain guidance from FDA regarding the development plans for these products, in addition to the requirements already discussed for canagliflozin monotherapy. J&J submitted six specific questions to FDA, some having multiple components. On August 26, 2010, the Agency sent preliminary comments to the sponsor. Based on the FDA responses, J&J decided that additional clarification was required for only three questions (#4, #5B, and #6).

For convenience, all the questions and pre-meeting responses are repeated below, in normal font. The meeting discussion follows in **bold** font.

Please note that the sponsor submitted their meeting minutes on September 3, 2010. The amendment included a post-meeting clarification for question #4 and a follow-up question related to #5B. These items are identified by *italics*. Our response to the post-meeting question is underlined and in bold font.

Questions and Discussion

Questions Related to the CANA/MET XR FDC

Chemistry, Manufacturing and Controls

Question 1 — CM&C — CANA/MET XR FDC

For dissolution testing of the metformin component of the CANA/MET XR FDC tablet containing J&J metformin XR, the sponsor plans to either use 1 of the 9 established US Pharmacopeia (USP) methods or develop and validate an in-house method, as appropriate. In the New Drug Application (NDA) submission, the sponsor will propose and justify appropriate acceptance criteria for the metformin dissolution profile based on information obtained during development, including formulation considerations and process experience. Does the Agency agree with the proposed approach for developing the metformin dissolution method and acceptance criteria?

Agency Response:

Please submit your dissolution method development report (for both Cana and Metformin) for review as soon as it is available to obtain feedback from the agency.

Meeting Comments: No further discussion

Preclinical

Question 2 — Nonclinical Toxicology — CANA/MET XR FDC

The highest daily dose of the CANA/MET XR FDC (300 mg canagliflozin and 2,000 mg metformin XR) formulated with J&J metformin XR contains (b) (4) polymer (b) (4) at levels of (b) (4) mg (b) (4) per tablet corresponding to (b) (4) mg (b) (4) per day. Does the Agency agree that based on the existing safety information for (b) (4) additional preclinical studies are not required to be conducted for registration of the CANA/MET XR FDC formulated with J&J metformin XR?

Agency Response:

We agree that additional preclinical studies with (b) (4) polymers are not required for registration of the Cana/Met XR formulation.

Meeting Comments: No further discussion

Clinical Pharmacology

Question 3A — Drug-drug Interaction — CANA/MET XR FDC

To address the Agency's response at the EOP2 meeting [Q25] regarding doses in a metformin/canagliflozin drug-drug interaction (DDI) study, the sponsor will conduct such a study with metformin IR 2,000 mg and canagliflozin 300 mg (the highest intended daily CANA/MET XR FDC dose). Does the Agency agree that the design of the proposed Phase 1 DDI study evaluating canagliflozin 300 mg with metformin IR 2,000 mg will provide sufficient data for assessment to support the CANA/MET XR FDC tablet NDA?

Agency Response:

The proposed Phase 1 drug interaction study between 300 mg canagliflozin and 2000 mg metformin IR appears acceptable.

Meeting Comments: No further discussion

Question 3B — Bioequivalence — CANA/MET XR FDC

Does the Agency agree that the design of the proposed Phase 1 bioequivalence study with a 505(b) approved metformin XR reference product, conducted only under fed conditions, will provide sufficient data for assessment to demonstrate that the CANA/MET XR FDC tablet is bioequivalent to the individual canagliflozin and metformin XR components?

Agency Response:

It is acceptable to conduct the bioequivalence study between CANA/MET XR FDC tablet and individual canagliflozin and metformin XR components under fed conditions. The individual metformin XR tablet should be the U.S. approved product.

Meeting Comments: No further discussion

Question 3C — Posology — CANA/MET XR FDC



Agency Response:

If canagliflozin is administered once a day immediately prior to the morning meal in the Phase 3 studies, this means that canagliflozin is administered under fasting conditions. Hence, the Food Effect Study would be the support for the proposal to administer the CANA/MET XR FDC with



Meeting Comments: No further discussion

Clinical

Question 4 — Clinical — CANA/MET XR FDC

Does the Agency agree that the proposed Phase 1 studies to specifically support the CANA/MET XR FDC tablet (bioequivalence, DDI, and food effect) and the Phase 3 studies, in which once-daily canagliflozin is added to ongoing therapy with metformin (studies DIA3006 and DIA3009) or ongoing therapy with metformin and a sulfonylurea (SU) (DIA3002) or ongoing therapy with metformin and pioglitazone (DIA3012) or ongoing therapy with insulin (DIA3008 glycemic substudy in subjects receiving insulin monotherapy or insulin combination therapy with stable doses of any antihyperglycemic agent (AHA), including metformin), are

adequate to provide sufficient data to assess safety and efficacy and support the proposed US Package Insert indications for the CANA/MET XR FDC tablet?

Agency Response:

No, we do not agree. Since the CANA/MET XR FDC will be a new product and is an extended release formulation, you should provide pharmacokinetic information upon multiple-dose CANA/MET XR FDC tablet administration as well as the information for the potential of in vitro alcohol interaction with CANA/MET XR FDC.

The specific indication will be an issue for review. We anticipate that if the NDA does not provide clinical trial data to support treatment of diabetics who do not have adequate glycemic control on diet and exercise alone, CANA/MET XR FDC may be indicated only for patients already on either monotherapy, [REDACTED] (b) (4)

Please also clarify that you are planning to use currently approved metformin IR and XR products for these proposed studies.

Meeting Comments:

The Division reiterated that a study on the effects of alcohol was needed due to concerns related to “dose-dumping.” An *in vitro* study is sufficient if the results are negative, however, if there are any positive results, an *in vivo* trial will be required.

FDA noted that they would provide guidance for design of the *in vitro* study. (See attachment at the end of this document.)

The sponsor asked about the multiple dose PK study required to characterize the FDC product. The Division noted that a single-dose study was not sufficient because some multiple dose PK of modified-release formulations can not be predicted from a single dose PK. Only one strength of the product should be sufficient to be tested. The highest dose being studied is a reasonable dose to use.

The sponsor stated they would use 150 mg canagliflozin / 1000 mg XR metformin.

Post-Meeting Clarification:

The following comment was not discussed at the meeting, the Sponsor would like to provide clarification regarding the Agency’s comment “Please also clarify that you are planning to use currently approved metformin IR and XR products for these proposed studies.”

The reference product to be used in the proposed Phase 1 studies (bioequivalence and DDI) to specifically support the CANA/MET XR FDC tablet will be the FDA approved metformin IR (Glucophage) and metformin XR products (Glucophage XR or Glumetza).

The metformin product used in the ongoing Phase 3 combination studies are currently approved metformin IR and XR products in each respective country where the trials are being conducted.

Questions Related to the CANA/MET IR FDC

Clinical Pharmacology

Question 5A – Bioequivalence - CANA/MET IR FDC

Does the Agency agree that the design of the proposed Phase 1 bioequivalence study, conducted only under fed conditions, will provide sufficient data for assessment to demonstrate that the CANA/MET IR FDC tablet is bioequivalent to the individual canagliflozin and metformin IR components?

Agency Response:

It is acceptable to conduct the bioequivalence study between CANA/MET IR FDC tablet and individual canagliflozin and metformin IR components under fed condition. The individual metformin IR tablet should be the U.S. approved product.

Meeting Comments: No further discussion

Question 5B – Posology – CANA/MET IR FDC

Does the Agency agree that the design of the proposed Phase 1 pharmacokinetic/pharmacodynamic study in healthy volunteers, comparing canagliflozin twice daily dosing with canagliflozin once-daily dosing (at the same total daily dose), will provide sufficient data for assessment to bridge the safety and efficacy information obtained using the once-daily canagliflozin dosing regimen employed in the Phase 3 program to the proposed twice-daily dosing with the CANA/MET IR FDC?

Agency Response:

If canagliflozin is administered once a day immediately prior to the morning meal in the Phase 3 studies, this means that canagliflozin is administered under fasting conditions. Hence, the Food Effect Study would be the support for the proposal to administer the CANA/MET IR FDC with

(b) (4)

Your proposed development for bridging once-daily dosing with twice-daily dosing of canagliflozin is not sufficient unless there is a well established exposure-response relationship for plasma canagliflozin concentrations and HbA1C response for canagliflozin. The pharmacodynamic parameters you proposed to evaluate in the Phase 1 PK/PD study are useful for the development program, but insufficient for determining the efficacy of canagliflozin at this stage. Therefore, we recommend that you conduct an efficacy/safety clinical study to support the twice-daily dosing of canagliflozin.

Meeting Comments:

The Division clarified that the planned PK/PD study was not sufficient because the PD marker being used was not validated as a surrogate for efficacy.

The sponsor commented that they planned to evaluate the relationship between the PD markers (renal glucose threshold parameters) and HbA1C to develop a robust model where their proposed PD markers may meet the FDA definition of “well-established” surrogate for efficacy.

DMEP noted that the company would be taking a risk as they might still need to conduct a clinical study, after reviewing of the PK/PD data. However, FDA encouraged the firm to proceed with the PK/PD study and to submit the results to the Agency. The sponsor asked whether they can request as End of Phase 2A meeting or Type C meeting for the submission and review of the PK/PD data. The Agency responded that another meeting does not seem to be necessary at this time but if the sponsor submits the data and the evaluation results, Agency will review and call a meeting if it is needed.

With regard to a clinical study, the sponsor suggested a Phase 2 study, enrolling 60 - 80 subjects for 12 weeks, noting that 12 weeks should be sufficient to compare QD vs. BID dosing.

The Division commented that the 12-week treatment period was not sufficient to reliably detect HbA1c changes. The study may not need to be 24 weeks long but would need to be at least 16 – 20 weeks in length. 16 – 20 weeks was acceptable only if the data supported the equivalence of the IR formulation in terms of biomarkers. DMEP would still prefer a 24 week study.

In addition, the Division would request a robust design, adequately powered to demonstrate effect. The sponsor proposed 60 – 80 subjects per group for 16 – 20 weeks, noting that this design should provide sufficient power to demonstrate an effect compared to placebo.

Post-Meeting Comments and a Question from J&J

Based on the above dialogue and in lieu of conducting the proposed phase 1 PK/PD study, the Sponsor then described a 3-arm study with 60-80 patients per arm, at least 16 weeks in duration, in patients with T2DM, with 2 doses of canagliflozin (50 mg and 150 mg BID) and placebo (with the study drugs dosed twice daily with meals, as per the proposed posology), adequately powered to establish HbA1c-lowering relative to placebo. Does the Agency concur this is an acceptable design in accordance with the discussion at the meeting?

Agency response:

Yes, we concur this is an acceptable design in lieu of conducting the proposed phase 1 PK/PD study. We also encourage you to collect the PK and PD data from this efficacy trial and/or the Phase 1 PK/PD study.

Clinical

Question 6 – Clinical CANA/MET IR FDC

Does the Agency agree that the proposed Phase 1 studies to specifically support the CANA/MET IR FDC tablet (bioequivalence, pharmacokinetic/pharmacodynamic [once daily vs twice daily], DDI, and food effect) and the Phase 3 studies, in which once-daily canagliflozin is added to ongoing therapy with metformin (studies DIA3006 and DIA3009) or ongoing therapy with metformin and a SU (DIA3002) or ongoing therapy with metformin and pioglitazone (DIA3012) or ongoing therapy with insulin (DIA3008 glycemic substudy in subjects receiving insulin monotherapy or insulin combination therapy with stable doses of any AHA, including

metformin), are adequate to provide sufficient data to assess safety and efficacy and support the proposed US Package Insert indications in the proposed label?

Agency Response:

No, we do not agree. Please see our response to Question 5B regarding your proposed bridging study. If you cannot provide satisfactory exposure-response data as requested, you will need to conduct a 24-week-minimum clinical efficacy and safety study for twice daily canagliflozin dosing.

Meeting Comments: See discussion above.

Additional Regulatory Comments

505(b)(2) Applications

- We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see document FDA-2003-P-0274-0015 on <http://www.regulations.gov/search/index.jsp> responding to dockets FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Fixed-Dose Combination Products

- You will need to open separate new INDs for the IR and XR formulations of the fixed dose canagliflozin / metformin combination drug products prior to dosing subjects.

Minutes Preparer:

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Chair Concurrence:

Ilan Irony, M.D.
Diabetes Team Leader
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

BIOPHARMACEUTICS COMMENT - In Vitro Alcohol-Dose Dumping:

We recommend that you evaluate the alcohol induced dose dumping of your MR product. You should conduct in vitro drug release testing initially and you may have to follow-up with an in vivo study, depending on the result of the in vitro testing. You should discuss the result of your in vitro study with FDA prior to the NDA submission.

The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your MR product:

- *Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.*
- *The following alcohol concentrations for the in vitro dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.*
- *In general;*
 - *If the optimal dissolution medium is 0.1N HCl; dissolution profiles in this 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.*
 - *If the optimal dissolution medium is NOT 0.1N HCl; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.*
 - *If the optimal dissolution medium has not been identified; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.*
 - *If the dissolution of the MR product is pH independent; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.*
- *The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.*
- *The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).*
- *The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.*

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/s/

PATRICIA J MADARA
09/30/2010

Reference ID: 2843852

Reference ID: 3999284



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

IND 76,479

Johnson & Johnson Pharmaceutical Research &
Development, L.L.C.

Attention: Sukhdev K. Saran
Associate Director, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Saran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-28431754.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on April 28, 2009.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from End-of-Phase 2 meeting held on April 28, 2009



MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 28, 2009
TIME: 1:00 P.M. – 2:30 P.M.
LOCATION: White Oak Campus, Silver Spring, MD
APPLICATION: IND 76,479
DRUG NAME: JNJ-28431754 Oral
TYPE OF MEETING: End-of-Phase 2; Type B

MEETING CHAIR: Mary Parks, MD

MEETING RECORDER: Julie Marchick, MPH

FDA ATTENDEES:

Division of Metabolism and Endocrinology Products

Mary Parks, MD	Director
Hylton Joffe, MD, MMSc	Clinical Team Leader, Diabetes Team I
Ilan Irony, MD	Acting Clinical Team Leader, Diabetes Team II
Somya Verma, MD	Medical Officer
Eileen Craig, MD	Medical Officer
Karim Calis, PharmD, MPH	Clinical Analyst
Todd Bourcier, PhD	Pharmacology/Toxicology Team Leader
Fred Alavi, PhD	Pharmacology/Toxicology Reviewer
Julie Marchick, MPH	Regulatory Project Manager

Office of Biostatistics

J. Todd Sahlroot, PhD	Deputy Division Director
Wei Liu, PhD	Reviewer

Office of Clinical Pharmacology

Wei Qiu, PhD	Acting Clinical Pharmacology Team Leader
Johnny Lau, PhD	Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Kathleen Basmadjian, PhD	Vice President, Regulatory Affairs
William Canovatchel, MD	Sr. Director, Clinical Team Leader – Metabolism
Lindsay Cobbs, R.Ph.	Associate Director, Regulatory Affairs (FDA Liaison)
Jacqueline Coelln-Hough, R.Ph.	Sr. Director, Global Regulatory Affairs
Damayanthi Devineni, PhD	Director, Pharmacokinetics /Pharmacodynamics
Martin Fitchet, MD	Vice President, Internal Medicine

Mark Johnson, PhD	Director, Preclinical Development
Martin Kudlesky	Manager, Regulatory Affairs
Gordan Law, PhD	Director, Statistical Leader
Gang Li, PhD	Director, Biostatistics
Rao Mamidi, PhD	Director, Preclinical Development
Hamish Ross, PhD	Vice President, Clinical Research, Compound Development Team Leader
Sukhdev Saran, MBA	Associate Director, Regulatory Affairs
Wayne Shaw, DSL	Sr. Director, Clinical Project Scientist
Kirk Ways, MD, PhD	Vice President, Therapeutic Area Head - Metabolics

BACKGROUND:

IND 76,479 for JNJ-28431754 Oral was submitted by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. on April 25, 2007. JNJ-28431754 is a sodium-glucose co-transporter (SGLT2) inhibitor being studied for the treatment of type 2 diabetes mellitus (T2DM). JNJ-28431754 is also being studied under IND 76,481 for the treatment of obesity.

Proposed Phase 3 Clinical Program

Protocol 28431754DIA3002 – *A Randomized, Double-Blind, 3-arm, Parallel-Group, 26 Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin and Sulfonylurea Therapy*

Protocol 28431754DIA3004 – *A Randomized, Double-Blind, Placebo-Controlled, 2-arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Glycemic Efficacy and Renal Safety of JNJ-28431754 in the Treatment of Subjects With Type 2 Diabetes Mellitus and an Impaired Renal Function*

Protocol 28431754DIA3004 – *A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 26-Week, Multicenter Study with a 26 Week Extension to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled With Diet and Exercise*

Protocol 28431754DIA3006 – *A Randomized, Double-Blind, Placebo-Controlled, 4-Arm, Parallel-Group, 52-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Versus Sitagliptin and Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy*

Protocol 28431754DIA3008 – *A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (Cardiovascular Outcomes Trial)*

Protocol 28431754DIA3009 – *A Randomized, Double-Blind, 3-Arm, Parallel-Group, 156-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability, of JNJ-28431754 100 mg or*

JNJ-28431754 300 mg Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy

Protocol 28431754DIA3010 – *A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 in the Treatment of Subjects ≥ 60 Years of Age With Type 2 Diabetes Mellitus*

Protocol 28431754DIA3011 – *A Randomized, Double-Blind, 5-Arm, Parallel-Group, 26-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 in Combination with Metformin Extended-Release Tablets as Initial Combination Therapy in the Treatment of Subjects With Type 2 Diabetes Mellitus*

MEETING OBJECTIVES:

- To discuss the Sponsor's proposed Phase 3 clinical development program, including the Sponsor's proposed cardiovascular plan
- To discuss the Sponsor's proposed preclinical development program

DISCUSSION POINTS:

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's responses provided to the Sponsor on April 27, 2009, follow in bold. A summary of the meeting discussion is italicized.

Cardiovascular Outcomes Trial

Question 1: Statistical Analysis

- A. Does the Agency agree with the proposed definition of the composite primary endpoint?

Response: The Sponsor is proposing a composite primary endpoint of cardiovascular (CV) death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for acute coronary syndrome, and new-onset heart failure. While the Division recognizes that the December 2008 Guidance to Industry *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* discusses the possibility of including CV events other than CV death, myocardial infarction, and stroke, the Division encourages a more traditional Major Adverse Cardiovascular Event (MACE) composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. The Division recommends a more traditional MACE endpoint because it is not convinced that hospitalization for acute coronary syndrome or new-onset heart failure is equally weighted to the other composite endpoints of CV death, nonfatal myocardial infarction, and nonfatal stroke. Should the Sponsor proceed with the proposed composite endpoint, the contribution of each component of the composite endpoint to the overall findings will be a consideration to whether the Sponsor has ruled out an unacceptable cardiovascular risk associated with JNJ-28431754. Reference is made to the

additional comments at the end of this document for other considerations regarding CV assessment in the phase 2/3 program.

Meeting Discussion: The Division stated that they are in the process of standardizing the definitions for cardiovascular (CV) events of interest for diabetes trials and will communicate these definitions to sponsors at a later date.

The Division stated that the Sponsor should use a checkbox approach (rather than using open-ended questions) for capturing important information on CV events to ensure there is adequate information on these events for adjudication. The Sponsor proposes to submit the adjudication charter with the final protocol.

The Sponsor plans to adjudicate all venous thromboembolic events because of the report of pulmonary embolism occurring in the phase 1 program. The Division agrees.

- B. Does the Agency agree with the proposed approach to rule out the risk ratio of 1.8 as detailed in the meta-analysis SAP?

Response: There are several potential sources of multiplicity that must be addressed including two dose groups, planned design adaptations and up to two interim analyses to rule out the 1.8 margin (the Division notes that Appendix 3.5 of the briefing document states that a Lan-DeMets spending function approach will be used to adjust for 2 interim analyses; however, other statements indicate there will be no such adjustment). With respect to dose, the primary analysis should be conducted on the combined dose arms. The design adaptations (dropping a treatment arm or randomizing additional subjects and extending the trial to show benefit) will also increase the type 1 error above the familywise error rate of 5%. The Division suggests that the Sponsor conduct a simulation study to determine the operational properties (e.g., type 1 error rate) for the proposed design and that the Sponsor submit the results of the simulation study for FDA review well in advance of the start of the clinical trial.

Meeting Discussion: Details concerning the impact of the potential sources of multiplicity on type 1 error were not discussed at the meeting. Instead, the Sponsor will submit a protocol to address the Division's specific concerns. The sponsor briefly discussed their overall plan to assess CV risk for canagliflozin. An initial meta-analysis (MA) will be conducted when there are 140 primary CV events across the program for the purpose of ruling out a hazard ratio (HR) of 1.8. If this HR is ruled out, the results will be submitted to the Agency as part of the NDA. The Sponsor will perform another meta-analysis at the end of the NDA review period to either discontinue an active treatment arm or randomize additional patients and extend the trial duration in order to demonstrate the superiority of canagliflozin to placebo on the MACE endpoint. The final MA will be conducted on 840 CV events to rule out a HR of 1.3

The Division agreed to the sponsor's plan to submit a separate Statistical Analysis Plan for the meta-analysis of subgroups across the Phase 3 program.

The Sponsor agreed to conduct a simulation study and submit to the Division the simulation code and the results of the simulation, including assessment of the operational properties of the design. .

- C. Does the Agency agree with the proposed approach to rule out the risk ratio of 1.3 as detailed in the meta-analysis SAP?

Response: See response to Question 1B.

Meeting Discussion: See discussion under Question 1B.

Question 2: Glycemic Control Analysis in Sub-Studies

- A. Does the Agency agree with the proposal to demonstrate the efficacy and safety of JNJ-28431754 in combination with patients inadequately controlled either on insulin or on a sulphonylurea and the planned 2-sided significance level of 0.05 on each sub-study?

Response: This proposal is acceptable to evaluate the efficacy of each sub-study at the 5% alpha level and to evaluate safety. As part of the efficacy evaluation, the Sponsor should continue to collect glycemic measurements if a patient experiences a primary CV endpoint. Within each sub-study, the Sponsor should adjust the Type 1 error rate for multiple doses. When the Sponsor submits the complete protocol for FDA review, the Sponsor should include the minimum number of JNJ-28431754-treated patients in each of these sub-studies who the Sponsor anticipates will be exposed to study drug for at least 1 year.

Meeting Discussion: The Sponsor stated that they will continue to collect glycemic measurements for all patients, unless the patient withdraws consent.

- B. If acceptable efficacy & safety is demonstrated in these predefined sub-groups, does the Agency agree these can support the basis for primary indications of usage in these treatment combinations or, at minimum, preclude any limitations for use in the labeling due to absence of safety information in these populations?

Response: The Division agrees, but if the Sponsor is seeking an indication in a subgroup, the study should be designed to display safety and efficacy in this group from the onset.

Meeting Discussion: None

Question 3: Stratification

Does the Agency agree with the proposed stratification variables for randomization (regional location of the clinical site and the use of background anti-diabetic medications) in the CV outcomes trial?

Response: Yes

Meeting Discussion: None

Question 4: Proposal to adapt the CV outcomes trial to eliminate a dose group of randomize additional subjects to demonstrate cardiovascular protection

- A. Pending results of either planned interim analysis for the CV study, does the Agency agree that a JNJ-28431754 treatment group could be eliminated and subjects in this treatment group discontinued from the study?

Response: See response to Question 1B

Meeting Discussion: None

- B. Does the Agency agree that under the direction of the IDMC and based on pre-specified criteria, the design of the ongoing trial could be modified using pre-specified guidelines to allow randomization of additional subjects into either one or both of the JNJ-28431754 treatment groups to assess the ability of JNJ-28431754 to reduce CV events?

Response: See response to Question 1B.

Meeting Discussion: None

- C. If a CV protective effect was demonstrated in one or both JNJ-28431754 dose arms, could an indication relevant to the reduction in cardiovascular events be obtained?

Response: Yes

Meeting Discussion: None

- D. Under what premise could the Sponsor obtain further input from the Agency or collaborate with the Agency on this strategy?

Response: The Sponsor may submit the proposed protocol, along with any questions, to the IND for review. Such a submission could be part of a meeting request, but the Division will decide on a case-by-case basis whether to grant such a meeting or respond in writing to the questions, depending on the nature of the questions and the complexity of the subject matter.

Meeting Discussion: None

Question 5: Collection of Adverse Events

Does the Agency agree with the proposal to analyze, in accordance with the FDA Critical Path Initiative, only serious adverse events, non-serious adverse events causing study drug discontinuation, and predefined adverse events of special interest for the post-NDA approval Phase of the CV outcomes trial?

Response: Yes. The Division also agrees with the Sponsor's plan to have investigators continue to routinely record all adverse events on the source documents held at the investigative sites in the event a safety question is raised in the future that could not be addressed with the data on file at the Sponsor.

Meeting Discussion: None

Question 6: Reporting of Adverse Events

Does the Agency agree that for purposes of reporting serious adverse experiences from this CV outcomes trial, the components of the clinical primary composite endpoints will not be considered adverse events or serious adverse events and will not be considered as unexpected but as disease related and will not be unblinded or subject to expedited reporting?

Response: Yes, particularly because these events will be monitored by an Independent Data Monitoring Committee on an ongoing basis.

On page 42 of the briefing document, the Sponsor mentions that all other serious, unexpected adverse events will be unblinded. The Division does not recommend that all these other events be unblinded as this could affect trial integrity. The decision of whether to unblind such events should be made on a case-by-case basis.

Meeting Discussion: None

Post-Meeting Comment: On June 18, 2009, the Sponsor sent the following clarifying question by email to the Division: "Does the Agency's preliminary response above apply only to the CV study (DIA3008) or to all of the planned phase 3 studies? Please note that CV events from all clinical trials will be adjudicated." The Division responded by email on June 23, 2009, that this response applies to all of the phase 3 studies.

Question 7: Reduction of Renal Risk

A secondary objective of the CV outcomes trial will be focused on reduction of renal risk (defined as a composite of progression to micro-albuminuria, progression to macro albuminuria, decline in estimated GFR to <30 mL/min/1.73m², halving of estimated GFR, requirement for renal replacement therapy, or renal death). Does the Agency agree that this analysis will, if successful, (b) (4) versus placebo as proposed in the USPIs for JNJ-28431754 and the Fixed Dose Combination (FDC) of JNJ-28431754 and metformin?

Response: The Division does not agree. What the Sponsor is proposing is not considered a clinically meaningful endpoint (b) (4) Macro and microalbuminuria are not well-validated surrogates of renal disease progression. At this time, the Division would accept a composite endpoint based on the doubling of serum creatinine, equivalent of halving of glomerular filtration rate, and progression to endstage renal disease or dialysis. Other renal endpoints could include

progression to microalbuminuria, progression to macroalbuminuria, or renal death. The complete protocol should define all these terms, including renal death.

Meeting Discussion: The Sponsor asked whether it would be useful for prescribers to know from the label whether patients progress to microalbuminuria vs. macroalbuminuria. The Division stated that the Sponsor should submit a proposal, which the Division will discuss with the Cardio-Renal Division.

Safety

Question 8: Renal Safety

- A. Does the Agency agree that the proposed clinical plan will provide sufficient data to characterize the renal safety of JNJ-28431754?

Response: The Sponsor is proposing a dedicated renal safety study in patients with moderate renal impairment and will include patients with, at most, mild renal impairment in the other phase 3 trials. The Sponsor is asked to provide an estimate as to the anticipated number of JNJ-28431754-treated patients with mild renal impairment (eGFR assessed by the MDRD formula 50-80 mL/min) who will be exposed to study drug for at ≥ 1 year, ≥ 2 years, and ≥ 3 years in the phase 2/3 program. The Sponsor is also asked to clarify why they will not be enrolling patients with moderate renal impairment in the general phase 2/3 program.

For this trial, the Sponsor is proposing a 26-week double-blind core trial followed by a 26-week double-blind extension trial. The extension trial should not be voluntary – i.e., all patients who complete the core trial should participate.

Currently, the Sponsor is only proposing to enroll approximately sixty JNJ-28431754-treated patients in the dedicated renal safety trial. This exposure is too small. The Sponsor should ensure that at least 150 JNJ-2843174-treated patients complete at least 26 weeks of treatment and that at least 100 JNJ-2843174-treated patients complete 1-year of treatment.

Meeting Discussion: The Sponsor presented a slide showing the estimated number of patients with mild and moderate renal impairment who will be exposed to the study drug for ≥ 1 year, ≥ 2 years, and ≥ 3 years (see slides attached to the end of this document). The Sponsor asked if it would be acceptable to not study patients with severe renal impairment. The Division stated that this would be acceptable because it is not expected that the study drug will have efficacy in this population based on the product's mechanism of action. This important limitation of use will be reflected in labeling. Although exposures to study drug are increased approximately 50% in patients with moderate renal impairment, the Sponsor is interested in studying the 300 mg dose in patients with moderate renal impairment. The Division supports this approach if there are adequate non-clinical safety margins and the phototoxicity concerns are addressed. Obtaining safety data with the 300 mg dose in patients with moderate renal impairment is encouraged because some patients with moderate renal impairment are likely to be

inadvertently exposed to the 300 mg dose of the product, if approved, if a healthcare provider relies only on serum creatinine as an estimate of renal function or if renal function deteriorates between clinic visits.

- B. Does the Agency agree that the design of the proposed study and the dose selection will provide sufficient data to evaluate the safety and efficacy of JNJ-28431754 in patients with renal impairment as defined by an eGFR of ≥ 30 ml/min/1.73m² and < 60 ml/min/1.73m²?

Response: The Sponsor should define moderate renal impairment as eGFR 30-50 mL/min based on the MDRD formula.

The Division recommends that the Sponsor obtain timed urine collections (to provide a more robust estimate for glomerular filtration rate and urinary protein excretion) in at least a subgroup of patients in this trial. In the development program, the Sponsor should also consider measuring translational biomarkers of renal injury (e.g., urinary beta-2-microglobulin, urinary cystatin C). For more information on translational renal biomarkers, the Sponsor can contact Bill Mattes at C-PATH through <http://c-path.org/>.

The Division recommends that the Sponsor stratify randomization by background antidiabetic therapy.

Meeting Discussion: The Sponsor acknowledged the recommendation to obtain timed urine collections. The Sponsor will submit a proposal that the Division will discuss with the Cardio-Renal Division.

- C. Does the Agency agree with the proposal to not study subjects with an eGFR less than 30 ml/min/m² and to not recommend the use of JNJ-28431754 in patients with severe renal impairment, end stage renal disease or those on dialysis?

Response: This proposal is reasonable. There is no single serum creatinine value that can be used for all patients to reliably distinguish the various degrees of renal function. Patients with reduced muscle mass, such as women or the elderly, can have normal or only slightly elevated serum creatinine measurements despite the presence of moderate or severe renal impairment (Arch Intern Med. 2003; 163: 356-360). Because serum creatinine is widely used as a marker of renal function, some patients with severe renal impairment could inadvertently be exposed to JNJ-28431754 even if JNJ-28431754 is not approved for use in this population. This limitation will need to be taken into consideration if JNJ-28431754 has significant toxicity in patients with any degree of renal impairment.

Meeting Discussion: None

- D. Does the Agency agree to using the Modification of Diet in Renal Disease (MDRD) equation for evaluation of glomerular filtration rate in patients enrolled to the Phase 3 studies, and subsequently in the USPI?

Response: The Sponsor should measure serum creatinine via a standardized assay [W.G. Miller *Am J Kid Dis* 52:645-8 (2008)]. The Division agrees with the approach to categorize renal impairment based on the MDRD equation. As supportive analyses, the Sponsor is asked to also present the renal function, efficacy, and safety data via the Cockcroft-Gault equation.

Meeting Discussion: None

Question 9: Bone Safety

Does the Agency agree that the proposed clinical plan, including a study using DEXA to assess bone mineral density, will adequately characterize bone safety of JNJ-28431754?

Response: No. Study DIA3010 will only obtain bone safety assessments in patients receiving up to 52 weeks of treatment. The Division recommends that the Sponsor incorporate bone safety evaluations (e.g., bone mineral density testing, bone biomarkers, vertebral x-rays) in a substudy of the longer-term cardiovascular trial.

Meeting Discussion: The Sponsor suggested following patients for 2 years to obtain long term safety data in a dedicated trial rather than having a separate substudy in the cardiovascular trial. The Division asked what proportion of patients will be on pioglitazone. The Sponsor said that they would provide that information at a later time. The Sponsor plans to set up a bone adjudication committee and establish pre-defined adjudication criteria.

As for additional non-clinical data, if the Sponsor conducts mechanistic studies, the Division would be interested to see the results but does not have any specific recommendations. The Division inquired about potential inhibition of SGLT1 in bone, but the Sponsor stated that drug concentrations would not be sufficiently high in blood to cause SGLT 1 inhibition in bone. The Division also stated that non-clinical mechanistic data may not adequately address the clinical relevance of the animal findings or reduce the need for adequate evaluation in human subjects.

The Division stated that limitations of the Sponsor's current proposal include (1) an assumption that the bone mineral density data will reflect bone strength and (2) that non-inferiority margins used in bone efficacy trials may not be appropriate for an assessment of bone safety.

The Division will provide more comments to the Sponsor after the Sponsor submits the protocol.

Question 10: Evaluation of Photosensitivity Potential

Does the Agency agree that the preclinical and clinical assessments of photosensitivity and skin safety of JNJ-28431754 both conducted and planned will be adequate to fully

characterize the photosensitivity potential and skin safety of JNJ-28431754 and support the proposed labeling?

Response: Additional nonclinical studies are not recommended as the completed studies have adequately identified and characterized the phototoxic potential of a JNJ-28431754. The clinical approach is reasonable, but further comments may be forthcoming after the Sponsor has submitted complete protocols for the planned clinical assessments.

Meeting Discussion: None

Question 11: Hypoglycemia

Does the Agency agree with the plan for reporting and analysis of hypoglycemic events?

Response: The protocols should include patient education on symptoms of hypoglycemia. Patients should be instructed to measure and record blood glucoses if such symptoms are experienced.

Meeting Discussion: None

Efficacy

Question 12: Comparison to Sitagliptin

Does the Agency agree that the designs of the two proposed studies (DIA3006 and DIA3002) to assess the superiority of JNJ-28431754 to sitagliptin on glycemic control and bodyweight are appropriate and pending results the data could be included in both proposed USPIs (JNJ-28431754 and FDC) and promotional material?

Response: Tests to assess non-inferiority and superiority may be conducted without alpha penalty in the same study if the non-inferiority margin is pre-specified and the same statistical test result (confidence interval) is applied to both hypotheses. The Division defers labeling discussions until after the NDA has been reviewed.

Meeting Discussion: None

Question 13: Study "Run-in" Period

Does the Agency agree that the optimization approach described to facilitate subject enrollment is acceptable?

Response: Yes.

Meeting Discussion: None

Statistics

Question 14: Subgroup Analyses

Does the Agency agree that data from the proposed meta-analyses of change in blood pressure and HbA1c for all subjects across Phase 3 glycemic assessment studies and also within predefined subgroups of subjects with high baseline blood pressure and HbA1c will provide sufficient data for inclusion of the subgroup analysis results in both proposed USPIs (JNJ-28431754 and FDC)?

Response: The Sponsor should apply family-wise type I error control to address all important statistical results/statements intended for the label, including secondary endpoints, subgroups and statements generated by secondary hypotheses. The final decision regarding labeling will be made after the NDA has been reviewed.

Meeting Discussion: The Sponsor plans to submit the meta-analysis plan. This will be separate from the Statistical Analysis plan. The Division stated that this is acceptable.

Question 15: Operational Plan for Study Extension

The NDA submission will include 26 week data from all studies with the exception of DIA3009 which will have 52 week data and DIA3008 which is event driven. Does the Agency agree with the proposed general operational plan for the study extensions, in which the Sponsor will break the treatment blind at the time of primary endpoint (26 weeks in all studies except DIA3008 and DIA3009, while still maintaining the blind for the investigators and the subjects through to the end of study extensions)?

Response: The Sponsor is asked to clarify why the extension trials will not be completed at the time of NDA submission given that the NDA submission will only take place after there are sufficient data from the cardiovascular safety trial and 52-week data from DIA3009. For extension trials that will be completed prior to NDA submission, the Division strongly recommends that the blind for the corresponding core trials not be broken until after the extension is complete.

The Division strongly recommends that all extension trials not be voluntary (i.e., all patients who complete the core trials should participate).

Meeting Discussion: None

Question 16: Phase 3 Clinical Program

Does the Agency concur that the studies included in the proposed Phase 3 clinical development program through their respective primary endpoint durations comprise a complete package with adequate exposures to characterize the benefit/risk ratio in support of a New Drug Application filing of oral immediate-release JNJ-28431754 for the proposed indication and proposed USPI?

Response: Reference is made to the response to Question 15. The Sponsor is asked to clarify why they are not conducting an add-on to thiazolidinedione phase 3 efficacy and safety trial? Thiazolidinediones have been associated with fractures, particularly in women. Therefore, the Sponsor should assess bone safety in a reasonable number of patients treated both with JNJ-28431754 and a thiazolidinedione.

Meeting Discussion: The Sponsor stated that they may conduct an add-on to thiazolidinedione (TZD) study later, but the study would not be complete by the time of NDA filing. The Division stated that TZDs are one of the most commonly used oral anti-diabetic medications and that it would be important to obtain efficacy and safety information in this setting. If there are inadequate or no add-on to TZD data at the time of NDA filing, it would be noted in the labeling under Important Limitations of Use and the trial would likely be a post-marketing requirement because of the association of bone fractures with TZD therapy and the potential for adverse bone effects with JNJ-28431754. For the reasons stated above, the Sponsor was strongly encouraged to obtain adequate data in patients on TZD therapy pre-approval.

Question 17: Target Population

The Phase 3 clinical development program will be conducted globally. Does the Agency agree that a 25% proportion of randomized patients from North America is an appropriate target?

Response: The Division prefers that approximately one-third of randomized patients come from North America. Regardless, the entire studied patient population should resemble the U.S. population who will take JNJ-28431754, if approved.

Meeting Discussion: The Sponsor stated that the one-third of randomized patients from North America will also include patients from Mexico. The Division stated that this would be acceptable.

Question 18: Secondary Endpoints

The Phase 3 glycemic efficacy studies will have clinically relevant pre-specified secondary endpoints (e.g. change in weight, FPG). A hierarchical testing procedure will be developed to test the treatment differences (JNJ-28431754 vs. control) for the primary and secondary endpoints in each study to preserve the overall type 1 error rate. Does the Agency agree that these secondary endpoints pending results will provide sufficient data for inclusion in both proposed USPIs (JNJ-28431754 and FDC)?

Response: Type 1 error control for secondary endpoints will provide support for labeling. However, the final decision regarding what information is appropriate for the label is a review issue.

Meeting Discussion: None

Clinical Pharmacokinetic and Pharmacology

Question 19: Drug-Drug Interaction Study

A Drug-Drug interaction study (DIA1004) with glyburide (metabolized by CYP2C9) has been conducted and no clinically meaningful changes were seen. Does the Agency agree, given that warfarin is also metabolized by CYP2C9, that a drug-drug interaction study with warfarin is not necessary?

Response: No, the Division does not agree.

CYP2C9 primarily metabolizes (> 90%) S-warfarin [Stehle et al. *Clin Pharmacokinet* 47:565–94 (2008)]. Warfarin is a recommended in vivo CYP2C9 substrate per the Draft Drug Interaction Guidance [<http://www.fda.gov/cder/guidance/6695dft.pdf>].

Initial data in 1998 indicated that CYP2C9 primarily metabolizes glyburide [W. R. Brian Hypoglycemic Agents. In: Levy et al. editors. *Metabolic Drug Interactions*. Lippincott Williams & Wilkins; 2000 ed, p 529–43; Niemi et al. *Clin Pharmacol Ther* 72:326-32 (2002)]. However, recent in vitro studies show that CYP3A4 and CYP2C19 also metabolize glyburide [van Giersbergen et al. *Clin Pharmacol Ther* 71:253-62 (2002)] and that CYP3A4 mainly metabolizes glyburide [Naritomi et al. *Xenobiotica* 34:415-27 (2004)].

Meeting Discussion: None

Question 20: Food Effect – BA-BE Study

In completed Phase 1 studies (NAP1003 and NAP1001), minimal food effect has been observed with the suspension and Phase 2 tablet formulation. The Phase 3 program will utilize a virtually identical tablet formulation which is currently being evaluated in a comparative BA study. In the proposed Phase 3 trials, subjects will be advised to administer the dose immediately before the first meal of the day.

A. Assuming the results of the comparative BA study (DIA1017), demonstrate comparable rate and extent of absorption for the Phase 2 and Phase 3 tablet formulations, does the Agency agree that no additional food effect study at 100 mg and 300 mg doses is required with the to-be-marketed product?

Response: No, the Division does not agree. Reference is made to the Food Effect Guidance (<http://www.fda.gov/cder/guidance/5194fnl.pdf>) for details.

Study 2843175NAP1003 has the following issues:

Food Effect Guidance's Recommendation	Study 2843175NAP1003's Design
The highest strength of a drug product intended to be marketed should be tested.	The highest strength tested for food effect was the 200 mg JNJ-28431754 Phase 2 tablet formulation, whereas the highest to-be-marketed strength will be the 300 mg JNJ-28431754 tablet formulation.
A high-fat and high-calorie meal is recommended as a test meal.	No information on the meal content.
Fasting should be an overnight fast of at least 10 hours. No food should be allowed for at least 4 hours post-dose.	No information on the condition of fast for the participants who received the single 25 and 200 mg tablets. The fasted participants who received the 400 mg dose (2 x 200 mg tablets) received breakfast 30 minutes after dosing.
Following an overnight fast of at least 10 hours, participants should receive the dose right after the test meal.	Participants received the 25, 200, and 2 x 200 mg tablets 10 minutes before the breakfast.

In addition, there is one more assumption that the to-be-marketed tablet formulation will be identical to the clinically tested Phase 3 tablet formulation.

Study 2843175NAP1001 used the suspension formulation, which will neither be the Phase 3 clinical formulation nor the to-be-marketed formulation.

Meeting Discussion: None

- B. Since the food effect is minimal with the tablet formulation, does the Agency agree that any future BA/BE studies with the tablet formulation need not be conducted under fed conditions?

Response: Reference is made to the Bioavailability and Bioequivalence Guidance [<http://www.fda.gov/cder/guidance/5356fnl.pdf>] for the BA/BE studies' design.

Meeting Discussion: None

Nonclinical

Question 21: Metabolite Characterization

The major metabolic elimination pathway for the compound in humans is *O*-glucuronidation. The two major human plasma circulating metabolites M5 and M7 (two *O*-glucuronide conjugates of the parent) were not quantitatively measured in GLP toxicology studies. For pharmacokinetic characterization both metabolites were measured in humans at selected doses in different clinical studies.

- A. Does the Agency agree that the pharmacologically inactive *O*-glucuronides (M5, M7) have no safety relevance and need not be measured in completed or future nonclinical studies for safety exposure assessment?

Response: The Division agrees that the two *O*-glucuronidated metabolites (M5 and M7) are pharmacologically inactive for inhibition of SGLT2 and likely do not merit separate toxicological evaluation. However, the Division does not agree that the single low dose studies with radiolabeled parent drug adequately characterized generation of and exposure to M5 and M7 in preclinical species which were exposed to much higher doses of JNJ-28431754. Therefore, the Division requests that the Sponsor measure M5 and M7 in either the 3 month or chronic toxicology studies already completed to better characterize exposure to these metabolites in preclinical species. The Division also request that M5 and M7 be included in the toxicokinetic evaluation of mice in the 2 year carcinogenicity study. Confirmed exposure in the mice could address the lack of genotoxicity testing with M5 and M7.

Meeting Discussion: None

- B. Does the Agency agree that the available data is sufficient to characterize the clinical pharmacokinetics of JNJ-28431754 metabolites (M5, M7) and that no additional metabolite pharmacokinetic data need be generated in the future clinical trials for the product registration?

Response: The Division agrees.

Meeting Discussion: None

Question 22: Clinical Pharmacology and Pharmacokinetic Studies

Does the Agency agree that the completed clinical pharmacology and pharmacokinetics studies are sufficient to support the initiation of the proposed Phase 3 studies and that the completed, ongoing and planned clinical pharmacology pharmacokinetics studies comprise a complete package in support of Drug Application filing of oral immediate-release JNJ-28431754 for the proposed indication and both proposed USPIs (JNJ-28431754 and FDC)?

Response: The Sponsor should examine the following, *in vitro*, for the major circulating metabolites such as M5 and M7:

- inhibition and induction potential on major drug metabolizing cytochrome P450 isozymes
- substrate status as well as inhibition and induction potential on transporters

The Sponsor should address JNJ-28431754's enterohepatic recycling potential, since JNJ-28431754 is extensively metabolized to the M5 and M7 glucuronides which can undergo enterohepatic recycling in humans. Disruption of the enterohepatic recycling such as antibiotic coadministration may decrease systemic JNJ-28431754 exposure and cause efficacy concern.

The Sponsor should consider the following for the Phase 3 clinical studies:

- collect sparse blood samples such as trough JNJ-28431754 concentration samples so as to evaluate the effect of covariates such as age, gender, and ethnicity on JNJ-28431754 exposure via population pharmacokinetic analyses [<http://www.fda.gov/cder/guidance/1852fnl.pdf>]
- collect pharmacogenomic samples to further evaluate JNJ-28431754's variability in exposure since UGT1A9 metabolizes JNJ-28431754 and UGT1A9 shows polymorphism [Kiang et al. *Pharmacol Ther* 106:97–132 (2005)]

Pre-Meeting Response from Sponsor: On April 27, 2009, the Sponsor emailed the following response:

The clinical multiple dose DDI studies (DIA1009 - simvastatin; DIA1004 - glyburide; DIA1002 - Oral contraceptives) conducted thus far did not show any indication of induction of CYP3A4, CYP2C9 and CYP2C19. Further data from the two week multiple ascending dose studies did not indicate any possible auto-induction of drug metabolizing enzymes that are involved in the metabolism of JNJ-28431754 based on the exposure comparisons from Day 1 to Day 14.

In addition, induction potential is evaluated in human hepatocytes for JNJ-28431754 up to concentration of 10 μ M. Under these conditions M5 and M7 metabolites are formed rapidly at high amounts (M7 = ~28 % , M5 = 7 % after 2 h incubation) based on the results from the in vitro hepatocyte metabolism study (FK6320).

Therefore the sponsor considers that induction potential of M5 and M7 has been evaluated in the completed induction study for JNJ-28431754. Does this address the Agency's request of evaluation of induction potential of M5 and M7?

Post-Meeting Comment:

The Division's response regarding the assessment of M5 and M7's CYP induction potential follows:

- *The clinical multiple-dose DDI studies may involve the complex interplay of JNJ-28431754, M5, and M7 with UGT isozymes, CYP isozymes and transporters, which makes the interpretation of individual M5 and M7's CYP isozymes induction potential difficult.*
- *JNJ-28431754's major metabolism is via glucuronidation. If auto-induction were to occur then it should be the UGT isozymes' auto-induction rather than the CYP isozymes' auto-induction, which is not relevant.*
- *The Sponsor indicated (Meeting Package's page 16 and pre-Meeting April 27, 2009 response above) that Study FK6320 examined up to 4.4 μ g/mL (10 μ M) JNJ-28431754. Per the renal impairment study (28431754-DIA-1003), mean plasma JNJ-28431754 C_{max} is 1.475 μ g/mL upon an oral single 200 mg dose administration to healthy participants. The mean plasma JNJ-28431754 C_{max} upon the proposed oral 300 mg once daily dose*

administration will be higher than 1.475 µg/mL due to the higher dose and accumulation (mean $t_{1/2}$ = 17.4 h). Thus, Study FK6320 might not have examined a high enough JNJ-28431754 concentration to address JNJ-28431754's CYP induction potential in vitro.

In conclusion, the Sponsor has not adequately addressed M5 and M7's CYP induction potential. In general if the Sponsor can demonstrate that a drug is not a CYP3A inducer, it can be concluded that the drug is also not an inducer of CYP2C8, CYP2C9, or CYP2C19 per the draft Drug Interaction Guidance [<http://www.fda.gov/cder/guidance/6695dft.pdf>].

Additional comment on assessing JNJ-28431754's CYP induction potential follows:

- *If the clinical multiple-dose DDI studies (such as DIAs 1009, 1004, and 1002) are deemed inadequate to assess JNJ-28431754's CYP induction potential upon review of their full reports via future NDA submission, another JNJ-28431754 CYP induction study per the draft Drug Interaction Guidance may be warranted.*

Clarification regarding evaluation of transporter induction potential of M5 and M7:

- a) We are not clear on the request; can the Agency provide more information on the relevance to evaluate induction potential on transporters?
- b) Are there transporter(s) of particular interest? Can the Agency recommend an acceptable assay to evaluate the induction potential on transporters?

Meeting Discussion: The Division asked whether a dose proportionality PK study has been conducted. The Sponsor stated that they have not conducted a dose-proportionality PK study yet, pending selection of the Phase 3 dose.

Post Meeting Comments:

The Sponsor's proposal of not evaluating both M5 and M7's induction potential on transporters is acceptable because currently there is a lack of a standardized in vitro method to study the induction of transporters. In general, the Sponsor should pay attention to the potential interaction between renal transporters (such as hOAT and hOCT) and JNJ-28431754 because JNJ-28431754's site of pharmacological action is in the kidney.

Because JNJ-28431754 has chiral-carbon centers, the Sponsor should address whether JNJ-28431754 shows any chiral inversion via metabolism in humans.

Question 23: Non-Clinical Studies

A comprehensive non-clinical program has been conducted and additional studies have been planned. Does the Agency agree that the completed/planned ADME, safety pharmacology, genotoxicity and repeat dose toxicity studies are acceptable to support registration of JNJ-28431754 and that no additional studies will be required?

Response: The Division agrees that the completed and planned nonclinical studies are adequate to support NDA submission.

Meeting Discussion: None

Fixed Dose Combination (FDC)

Question 24: Preclinical-FDC

Does the Agency agree that the completed preclinical studies for the single agent JNJ-28431754 and the Company's proposed preclinical studies with the combination product will provide adequate data for the assessment of pre-clinical safety in support of the development and registration of the JNJ-28431754 plus metformin FDC product, and no additional preclinical studies will be required?

Response: The Division agrees that a 3-month toxicology and an embryofetal development study in rats with JNJ-28431754 in combination with metformin is adequate. The Division recommends that the embryofetal study include separate arms for JNJ-28431754 and metformin alone, in addition to the combination groups. It should be noted that if the studies identify new targets, additional preclinical studies may be needed.

Meeting Discussion: None

Question 25: Clinical

Does the Agency agree that the proposed clinical studies for JNJ-28431754 (DIA3002, DIA3006, DIA3011, Bioequivalence [BE] and Food Effects studies) and the completed drug-drug interaction study with metformin (NAP1004) will:

- A. Provide adequate data for the registration assessment of a JNJ-28431754 plus metformin extended release Fixed Dose Combination (FDC) product?

Response: The Sponsor is asked to clarify the FDC product's strengths that the Sponsor intends to market so the Division can further advise on the BE study design. If the amount of JNJ-28431754 is greater than 100 mg and the amount of metformin is greater than 1000 mg in the FDC product, the completed Study NAP1004 will not adequately address the drug-drug interaction between JNJ-28431754 and metformin.

The proposed Food-effect study for the Fixed Dose Combination tablet is acceptable to the Division. However, the Sponsor should study the highest strength of JNJ-28431754 and metformin in the to-be-marketed Fixed Dose Combination product.

Reference is made to the Bioavailability and Bioequivalence Guidance (<http://www.fda.gov/cder/guidance/5356fnl.pdf>) and Food Effect Guidance (<http://www.fda.gov/cder/guidance/5194fnl.pdf>) for details.

Meeting Discussion: The Sponsor has not yet decided which doses to study. The Sponsor-proposes a 5-arm study. The Division stated that the Sponsor can submit the protocol with questions and the Division will respond in writing.

- B. Provide adequate data to support the expanded indication for use of the FDC as initial treatment in patients inadequately controlled on diet and exercise alone?

Response: Note that the Division has streamlined the indication for drugs and biologics developed for the treatment of type 2 diabetes. Separate indications (e.g., monotherapy, combination with Drug A, combination with Drug B, combination with Drug C, initial treatment, etc.) with a single, simplified indication "Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." This indication will be qualified by language in other parts of the label (e.g., Important Limitations of Use, Contraindications, Warnings and Precautions, Adverse Reactions, Clinical Studies), as appropriate.

DIA3011 appears appropriate to obtain data on JNJ-28431754 coadministration with metformin in patients with inadequate glycemic control on diet and exercise. The Division may have additional comments after we have received the completed protocol for review. Labeling comments will be deferred until after the NDA has been reviewed.

Meeting Discussion: None

Pediatric

Question 26: Submission of Pediatric Data

The Sponsor intends to submit a Proposed Pediatric Study Request (PPSR) under the Best Pharmaceuticals for Children Act (BPCA) to the Agency to obtain a written request for pediatric exclusivity. Does the Agency concur with the proposal to defer submission of pediatric data, as required by the Pediatric Research Equity Act (PREA), for JNJ-28431754 as a treatment for T2DM mellitus until after a favorable benefit/risk in adults has been established at NDA approval?

Response: See the response to Question 27.

Meeting Discussion: See Meeting Discussion under Question 27.

Question 27: Partial Waiver

Does the Agency concur with the request for a partial waiver from PREA to exclude children under the age of 10 from the pediatric study plan?

Response (Questions 26 and 27): The request is reasonable. However, formal request for deferral and waiver with an accompanying rationale must be included in the NDA together with a proposed pediatric plan (e.g., synopses of proposed pediatric trials). This plan should include a timeline proposing when the finalized pediatric protocol(s) will be submitted to FDA, when the proposed pediatric trial(s) will start, and when the completed clinical study report(s) will be submitted to FDA. A final decision regarding

the requested deferral and waiver cannot be made until the Division discusses this request with the Pediatric Review Committee (PeRC) after we have completed review of the NDA.

Meeting Discussion: In an email dated April 27, 2009, the Sponsor stated that Drs. Dianne Murphy and Lisa Mathis presented at the Pediatric Dialogue Session: FDA and PhRMA April 14, 2009, and encouraged pediatric discussions earlier in the development process and suggested that sponsors begin discussions at EOP2 meetings.

The Division stated that it is difficult to provide meaningful input into the pediatric development plan at the present time, particularly because there are no approved SGLT-2 inhibitors and our understanding of the efficacy and safety of this class of compounds is very limited.

Question 28: PREA Study Proposals

Consistent with the current paradigm of first line use of metformin monotherapy for the treatment of T2DM in adolescents, the Sponsor proposes to conduct a 6-month placebo-controlled safety and efficacy study (with a 6 month extension) in adolescents, aged 10-17 years inclusive, inadequately controlled by metformin monotherapy. Does the Agency agree that this metformin combination study design, together with a study to evaluate the pharmacokinetics of JNJ-28431754 in pediatric patients, would fulfill the pediatric data requirement in patients with T2DM, as required by PREA for the single agent formulation? Additionally, does the Agency agree that a full waiver is justified for the JNJ 28431754/metformin Fixed Dose Combination formulation in pediatric patients aged 10-17 years?

Response: It is premature to discuss the design of the pediatric study at this time. See response under Question 26. To obtain a full waiver for the fixed-dose combination (FDC) product, the Sponsor should include the rationale in the FDC NDA. This rationale should meet at least one of the following and include appropriate supporting documentation:

- a. **Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed)**
- b. **The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested**
- c. **The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested**
- d. **Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed**

Meeting Discussion: None

Mechanism of Action

Question 29: SGLT1 Effect

Does the Agency agree that the proposed study designs, should they confirm that intestinal absorption of glucose is delayed and/or reduced is evidence of local SGLT1 inhibition, will provide sufficient data to support a statement on this additional mechanism of action in the proposed USPI?

Response: This will be a review issue.

Meeting Discussion: None

[Redacted] (b) (4)

The majority of patients with T2DM are overweight or obese. [Redacted] (b) (4)

[Redacted] Given the magnitude of the Phase 3 program for JNJ-28431754 (greater than 6800 subjects exposed), and the dose-related weight loss properties as confirmed in both the diabetes and obesity Phase 2b dose-ranging studies, DIA2001 and OBE2001, respectively, [Redacted] (b) (4)

[Redacted] (b) (4)

Response: No, this would not be sufficient.

In order for JNJ-28431754 [Redacted] (b) (4) the Division would expect the Sponsor to study the efficacy and safety of the drug in a broad patient population [Redacted] (b) (4) with and without type 2 diabetes. [Redacted] (b) (4)

[Redacted] (b) (4)

Meeting Discussion: None

Additional Comments:

- 1. The Division recommends that the Sponsor study the 50 mg JNJ-28431754 dose, in addition to the proposed 100 mg and 300 mg doses in the Phase 3 development program.**

Meeting Discussion: The Sponsor presented slides and explained their rationale for selecting the 100 mg and 300 mg doses. The Sponsor stated that Table 2, page 24, in the briefing package more accurately reflects the efficacy of the 50 mg dose because of the least square means assessment of - 0.5% difference in HbA1c rather than the unadjusted mean assessment of - 0.8% difference in Table 8. Therefore, the Sponsor concluded that the 50 mg JNJ-28431754 dose may not be as effective as the proposed 100 and 300 mg JNJ-28431754 doses. In addition, the Sponsor stated that the safety and tolerability of the 50 mg dose is equivalent to that of the 100 mg dose based on the available data to date. The Division stated that studying the 100 mg and 300 mg doses is acceptable but recommended that the Sponsor consider studying the 50 mg dose in some phase 3 trials in case a safety concern arises with the higher doses.

- 2. In Protocol DIA3002, the Sponsor is asked to confirm that all sulfonylurea doses at randomization will be at least one-half the approved, maximum recommended dose. The Sponsor is asked to clarify why they are not requiring all patients to be on the same background sulfonylurea.**

Meeting Discussion: The Sponsor presented a slide with the planned sulfonylurea doses at randomization. The Sponsor agrees that all sulfonylurea doses at randomization, except for glipizide, will be at least one-half the approved, maximum recommended dose. The maximum recommended daily dose for glipizide is 40 mg but the Sponsor states that 20 mg is commonly considered the maximum recommended daily dose and, therefore, chose 10 mg for the glipizide trial. The Division requested the Sponsor provide usage data for 10 mg vs. 20 mg of glipizide to inform our decision regarding the appropriateness of 10 mg for the glipizide trial.

- 3. In all phase 3 clinical trials, the Division recommends that the Sponsor exclude patients with fasting plasma glucose >270 mg/dL to reduce the likelihood for needing early glycemic rescue medications.**

Meeting Discussion: None

- 4. In some trials, the Sponsor is discontinuing patients who require glycemic rescue therapy. The Division recommends that these patients initiate glycemic rescue but remain in the trials to bolster the safety database. Safety analyses can be performed in two ways: prior to rescue and regardless of rescue. For efficacy analyses, measurements after glycemic rescue can be considered missing.**

Meeting Discussion: None

- 5. In some trials, the Sponsor has the following glycemic rescue criteria from Weeks 12-26: HbA1c >8% and change from baseline HbA1c >0.5%. The Sponsor is asked to clarify the reason for requiring both of these HbA1c criteria to trigger rescue.**

Meeting Discussion: The Sponsor presented a slide with their rationale. The Division recommended only introducing HbA1c rescue criteria later in the trial (after Week 26), rather than at Week 12, because the Division's experience with other development programs is that early HbA1c rescue criteria can result in substantial rescue prior to the primary efficacy endpoint, impacting trial integrity. The Division recommended that the glycemic rescue criteria proposed for Weeks 12-26 instead be implemented starting at Week 26. The Sponsor agreed.

- 6. For the monotherapy phase 3 trial, the entry criterion for HbA1c up to 10.5% is too loose, particularly for patients who will undergo washout of antidiabetic therapy.**

Meeting Discussion: None

- 7. There is a typographical error in the glycemic rescue criteria for the add-on to metformin trial (page 244) – the Sponsor is asked to correct in the complete study protocol to be submitted to FDA.**

Meeting Discussion: The Sponsor acknowledged the typographical error.

- 8. The Sponsor should predefine all cardiovascular endpoint events and include these definitions (together with the adjudication committee charter) in the complete phase 3 clinical protocols that will be submitted for FDA review.**

Meeting Discussion: None

- 9. The Sponsor should measure serum troponin in patients with creatine phosphokinase (CPK) > 2x upper limit of normal. Additionally, the investigator should report whether or not the subject is having any cardiac symptoms and a 12-lead electrocardiogram (ECG) should be performed at the time of the CPK elevation. If troponin is elevated, serial troponin measurements and 12-lead ECGs are recommended as is hospitalization and cardiology consultation, if necessary.**

Meeting Discussion: The Sponsor stated that the investigator will be alerted if a routine CPK measurement is elevated. Investigators will consider further work-up for cardiac causes based on the clinical situation (e.g., if the patient has symptoms that could be consistent with myocardial ischemia). The Division stated that this proposal is acceptable.

- 10. The above comments and recommendations on your proposed phase 3 clinical trials are based on protocol synopses. Additional comments may be forthcoming after the Sponsor has submitted the complete protocols for FDA review.**

Meeting Discussion: None

Additional Discussion Topic

SGLT2-Associated Pulmonary Embolus

The Sponsor asked whether the Division can provide any feedback on whether venous thromboembolism has been seen with other SGLT2 inhibitors. The Division stated that responses to our form letter requesting information on venous thromboembolic events have been received from most of the sponsors of SGLT2 inhibitors, and among the responses received, there is no evidence of an association between this class of study drug and venous thromboembolism – although most programs are in early stages of development.

ATTACHMENT:

Slides presented by Sponsor during the meeting

Minutes Preparer: Julie Marchick
Chair Concurrence: Mary Parks

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/s/

JULIE C MARCHICK
06/25/2009