

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204353Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204353

Trade Name Invokamet

Generic Name canagliflozin and metformin hydrochloride

Applicant Name Janssen Pharmaceuticals, Inc.

Approval Date, If Known August 8, 2014

### 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)(2)

c) 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.

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:

d) 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

e) 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# 204042 (canagliflozin)

NDA# 020357 (metformin)

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:

A Phase 2 study (DIA2003) that examined twice-daily dosing of canagliflozin (50 mg and 150 mg bid)

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

Investigation #2 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

Investigation #2 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 #2(c), less any that are not "new"):

same as the investigations listed in #2(c)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND # 110545 (cross reference IND 076479 and IND (b) (4) YES  !NO

! Explain:

Investigation #2 !  
!  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES  ! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe 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: Abolade (Bola) Adeolu

Title: Regulatory Project Manager

Date: July 28, 2015

Name of Office/Division Director signing form: Jean-Marc Guettier, MD

Title: Director

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ABOLADE ADEOLU  
08/08/2014

LISA B YANOFF  
08/08/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204353	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 Established/Proper Name: canagliflozin and metformin HCl Dosage Form: Tablet		Applicant: Janssen Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Abolade (Bola) Adeolu		Division: Metabolism & Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="text-align: center;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)               <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)</li> </ul> </li> </ul> <p>Date of check:</p> <p><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></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>August 8, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		CR on December 11, 2013
❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

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: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ 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> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: CR on 12/11/13; AP on 8/8/14
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included. See labeling attached to approval letter.
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included. See labeling attached to approval letter.
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included. See labels attached to approval letter.
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	Invokamet: Acceptable 7/26/2013 and 5/2/2014 Letters: 5/2/2014; 7/26/2013 Reviews: 4/25/2014; 7/26/2013
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 2/20/2013 DMEPA: <input checked="" type="checkbox"/> 6/5/2014; 11/19/2013; 3/28/14; 6/5/14 DMPP/PLT: 8/1/2014 DRISK: 7/11/2014 OPDP: <input checked="" type="checkbox"/> 8/5/2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM: 2/20/2013
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	11/15/2013 and 7/22/2014
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	

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

<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	No
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	No
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>10/23/13</u> If PeRC review not necessary, explain: _____</li> </ul>	10/23/2013
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	12/28/2012; 2/16, 6/6, 6/17, 7/26, 8/30, 9/26, 10/30, 11/6, 11/13, and 11/18/2013; 12/11, 11/2/16, 1/10, 1/15, 1/24, 1/30, 2/19, 2/28, 3/28, 5/2, 6/9, 6/16, 6/26, 7/11, 7/21, 8/4 and 8/8/2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Clinical: 1/10/2014
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg WRO 8/30/2012
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	5/29/2013
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	9/12/2013
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	Type A meeting 12/19/2013
❖ Advisory Committee Meeting(s)	No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	None
Division Director Summary Review ( <i>indicate date for each review</i> )	8/7/2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	8/8/2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	3
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	7/23/2014, 11/1/2013; 2/10/2013;
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 15 of 11/1/2013 clinical review

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	REMS review by OSE: 7/11/2014, 11/14/2013
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	None
Statistical Review(s) ( <i>indicate date for each review</i> )	9/5/2013;2/25/2013; 1/25/2013;
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	; 7/20/2014; 11/15/2013; 2/7/2013;
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	9/17/2013;2/25/2013
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	None
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	6/10/2014; 8/21/2013; 2/1/2013; /
❖ 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
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	5/12/2014; 3/10/2014; 10/28/2013; 7/26/2013; 1/29/2013/1/2013; 8/21/2013; 6/10/2014
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	10/18/2013
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 9/25/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ 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	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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ABOLADE ADEOLU  
08/08/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Friday, August 08, 2014 4:31 PM  
**To:** 'Porter, Brandon [JRDUS]'  
**Subject:** RE: NDA 204353: labeling / Info for Call on Wed Aug 6th  
**Attachments:** FinalCanagliflozin-Metformin FDC USPI\_EDMS-ERI-44062552\_28 0 (clean).doc

Dear Brandon,

We accept your revisions to the label for NDA 204353 (canagliflozin/metformin IR tablets)

**Bola Adeolu**  
**301 796-4264**

---

**From:** Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]  
**Sent:** Friday, August 08, 2014 11:28 AM  
**To:** Adeolu, Abolade  
**Subject:** RE: NDA 204353: labeling / Info for Call on Wed Aug 6th

Hi Bola, here are the updated files to address the Agency comments.

Best,  
Brandon

---

**From:** Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]  
**Sent:** Friday, August 08, 2014 7:00 AM  
**To:** Porter, Brandon [JRDUS]  
**Subject:** FW: NDA 204353: labeling / Info for Call on Wed Aug 6th  
**Importance:** High

FDA has reordered the language slightly for increased readability. Please see attached edits. Also, it is unclear if the demographic data listed applies to the entire substudy population or to the subgroup of the substudy population.

**Bola Adeolu**  
**301 796-4264**

54 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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ABOLADE ADEOLU  
08/08/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Monday, July 21, 2014 2:20 PM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353: labeling

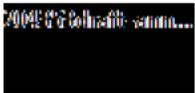
**Importance:** High

Dear Brandon,

Please find attached our initial comments/edits to the labeling for the canagliflozin/metformin application.

Kindly acknowledge receipt and let me know when to expect your response.

Thanks, Bola



Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
07/21/2014

## **Adeolu, Abolade**

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**From:** Adeolu, Abolade  
**Sent:** Friday, July 11, 2014 3:57 PM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353

Dear Brandon,

Please see the PMR/PMC list below and respond with dates by July 18, 2014.

**PMR/PMC list for NDA 204353  
INVOKAMET (canagliflozin and metformin fixed-dose combination) tablets**

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.

### **Postmarketing Requirement**

1. A study to evaluate whether pediatric patients with type 2 diabetes ages 10 to 17 years or healthy pediatric subjects ages 10 to 17 years can safely swallow INVOKAMET tablets. The study should evaluate tablets that are the same dimensions as the largest INVOKAMET tablet, and placebo tablets should be used if the study population consists of healthy subjects.

Final Protocol Submission:

Study Completion:

Final Report Submission:

Kindly acknowledge receipt of this email.

Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products

White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
07/11/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Thursday, June 26, 2014 3:39 PM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com); Saran, Sukhdev [JRDUS] (SSaran@its.jnj.com)  
**Cc:** Adeolu, Abolade; Chen, Elizabeth  
**Subject:** NDA 204353(cana-met)  
**Importance:** High

Dear Brandon,

We refer to your resubmission to the NDA 204353 dated Feb 10, 2014. We have following information request. Please submit the responses within 2 business days (**COB June 30, 2014**). If possible, please submit response to #2 by **COB June 27, 2014**.

1. Figure 6 of your exposure-response analysis report (Module 5.3.4.2) shows the mean HbA1c change from baseline profiles for QD and BID regimen. These profiles were generated using the baseline covariate values from Dataset 3 and conducting 100 simulations per individual subject, for each dose regimen. We would like to know how sensitive are the results to the number of simulations (N) conducted. Please generate similar profiles as in Figure 6 using 25 and 50 and 75 simulations. We are only interested in the results of the bridging and not the sensitivity analysis. For each of the scenarios mention the maximum difference in HbA1c between the regimens. For each scenario tabulate the mean and median of the baseline HbA1c for each dosing regimen.
2. In your simulations, steady-state concentration profiles were produced using the baseline covariate values from Dataset 3 and by simulating random effects from their estimated distribution (inter-subject variation). Additionally a set of model coefficients (fixed effects only) was generated from the corresponding asymptotic distribution of parameter estimates in the exposure-response model. Instead of simulating random effects from the IIV distribution, **use the post-hoc estimates** that were generated and simulate the steady-state concentration profiles for each dosing regimen. Similarly use **post-hoc estimates for PD parameters** as well and simulate the HbA1c for each individual for each dosing regimen. Based on this simulation provide the mean HbA1c profile for each dosing regimen similar to Figure 6. Mention the maximum difference in HbA1c between the regimens. Tabulate the mean and median of the baseline HbA1c for each dosing regimen.

Please copy Elizabeth Chen on all emails as I will be out of the office until July 8, 2014.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
06/26/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Monday, June 16, 2014 1:47 PM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Subject:** NDA 204353

**Importance:** High

Dear Brandon,

We refer to your response to our information request for NDA 204353 dated June 11, 2014. We have following information request. Please submit the responses by COB June 17.

Based on your IR, Table 3 shows that all subjects who are in the “metformin alone” stratum were selected for your analysis of study 3006 in order to generate Table 1 and Table 2 of the report. The analysis in the previous cycle excluded subjects who had dose-titration in the run-in period for the ‘Met only stratum’. Additionally your analysis included subjects despite absence of post-baseline HbA1c. These subjects were excluded in the previous analysis.

We recommend you to **not include these subjects in your analysis** and re-submit the following.

1. Table 1 and Table 2 showing results from studies 2003 and 3006.
2. Additionally for study 2003, submit results using ANCOVA model with treatment, glycemic control (whether HbA1c value  $\geq 8.0\%$ ), and baseline HbA1c as covariate as done in the previous cycle.
3. For 1 and 2 above, please submit the associated code in SAS.
4. Compare your findings from the above to the results presented in Table 1 of comparison of HbA1c report submitted in the previous cycle (Module 5.3.5.3).

Please acknowledge receipt of email

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

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/s/  
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ABOLADE ADEOLU  
06/16/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Friday, June 06, 2014 5:40 PM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353

**Importance:** High

Dear Brandon,

We refer to your resubmission to the NDA 204353 dated Feb 10, 2014. We have following information request. Please submit the responses within 2 business days.

1. Table 9 of your exposure-response analysis report (Module 5.3.4.2) shows the comparison of observed and model-predicted changes in HbA1c at the planned primary study endpoints for studies 2003 (i.e., week 18) and 3006 (i.e., week 26). Since the time for primary endpoint assessment was different between these studies, to facilitate review, please provide the observed and model-predicted changes in HbA1c at week 18 for study 3006.
2. Similarly since the time point for primary endpoint assessment were different between studies 2001 (i.e., week 12) and 2003 (i.e., week 18), please provide the observed and model-predicted changes in HbA1c at week 12 for study 2003.

For 1 and 2, provide LS Means for the change from baseline in HbA1C for the placebo and treatment arms, placebo-subtracted change from baseline, and number of subjects. Please submit the associated codes.

3. Compare your findings of the HbA1c comparison from the above to the results presented in Table 1 and Table 3 of comparison of HbA1c report submitted in the previous cycle (Module 5.3.5.3). Explain any observed differences and clarify if there are differences in the statistical models and the criteria used for selecting subjects for these analyses. Please submit all associated codes. If they were already submitted in the previous cycle, please direct us to the correct location.

Kindly acknowledge receipt of this email.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

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/s/  
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ABOLADE ADEOLU  
06/09/2014

From: Mistry, Mishale  
Sent: Thursday, June 05, 2014 9:07 AM  
To: Adeolu, Abolade  
Cc: Canida, Lyle; Maslov, Yelena  
Subject: Re: OSE Review # 2014-377-1 Invokamet (canagliflozin metformin) Labels and Labeling Review (NDA 204353)

Hello Bola,

DMEPA reviewed the updated container labels submitted on May 29, 2014 and noted that there are no concerns in terms of safety related to preventable medication errors. We compared the revised labels against the recommendations contained in OSE Review #2014-377, dated March 28, 2014 and determined that all of our comments were addressed.

DMEPA concludes that the proposed labels and labeling are adequate from a medication error perspective and therefore has no comments at this time.

Best,  
Mishale

Mishale Mistry, PharmD, MPH | Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)  
FDA/CDER/Office of Surveillance and Epidemiology  
10903 New Hampshire Avenue

(b) (6)  
Silver Spring, MD 20993  
Mishale.Mistry@fda.hhs.gov | Office: (240) 402-4577

From: Canida, Lyle  
Sent: Tuesday, June 03, 2014 12:17 PM  
To: Mistry, Mishale  
Cc: Maslov, Yelena  
Subject: NDA 204353 Canagliflozin and metformin labeling/ PI update

Hi Mishale,

A labeling update for NDA 204353 Canagliflozin and metformin is in.

Cover letter: \\cdsesubl\evsprod\nda204353\0023\m1\us\cover.pdf

Annotated draft labeling text: \\cdsesubl\evsprod\nda204353\0023\m1\us\draft-annot-labeling-text.pdf

eCTD sequence No. 0023

EDR link: \\cdsesubl\evsprod\nda204353\204353.enx

Thanks,  
Lyle

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/s/  
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LYLE CANIDA  
06/05/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 204353

**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 February 10, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Canagliflozin and Metformin HCl Tablets, 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1000 mg.

We also refer to your correspondence, dated and received March 11, 2014, requesting review of your proposed proprietary name, Invokamet.

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

If any of the proposed product characteristics as stated in your March 11, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lyle Canida, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1637. For any other information regarding this application, contact Abolade Adeolu, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
05/02/2014

## **Adeolu, Abolade**

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**From:** Adeolu, Abolade  
**Sent:** Friday, March 28, 2014 1:35 PM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353

Dear Brandon,

We recommend the following be implemented:

A. Container label

1. Relocate the warning statement “Store in the original container” to the principal display panel of the label and increase the size and prominence per Guidance: Container Labels and Carton Labeling, April 2013.

Relocating this warning statement may increase awareness to the importance of not removing Invokamet tablets from the original container or transferring to a pharmacy bottle or pill box since such actions may affect the product’s stability. As currently presented, this warning statement can be overlooked, which may impact the stability of the product.

Please acknowledge receipt, and plan to incorporate this recommendation once we begin labeling negotiations.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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ABOLADE ADEOLU  
03/28/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Friday, February 28, 2014 10:21 AM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Dear Brandon,

Please see the comments below with regards to the labeling for the canagliflozin/metformin application:

A. Insert Labeling

1. Under Dosage Forms and Strengths in the Highlights of Prescribing Information, Section 2 Dosage and Administration and Section 3 Dosage Forms and Strengths in the Full Prescribing Information, replace the slash symbol “/” used between the two ingredients with the word “and.” For example, revise “50 mg canagliflozin/500 mg metformin hydrochloride” with “50 mg canagliflozin **and** 500 mg metformin hydrochloride

B. Container Label

1. Revise the color scheme used to highlight and differentiate the strength statements. As currently presented, the strengths are not well differentiated and may cause product selection errors due to proximity in storage and similarity in trade dress:

i. For the 50 mg/500 mg strength, add color intensity to increase the prominence of that strength. As currently presented, the strength presentation is the same color as the proprietary name and established name and the box around the strength is barely visible, making it difficult to distinguish the strength of the product.

a. Revise the color scheme used to highlight the strength presentation of the 50 mg/1000 mg (b)(4) and 150 mg/500 mg (b)(4) to provide adequate differentiation. As currently presented the colors are similar and may cause product selection errors due to proximity in storage and similarity in trade dress.

ii. Revise the color scheme used to highlight the strength presentation of the 150 mg/1000 mg (b)(4) because this (b)(4) highlight is the same color used for the (b)(4) (b)(4). Ensure that the color scheme is not similar to any of the other color already used for (b)(4)

2. Relocate the statement “Each tablet contains xx mg Canagliflozin and xx mg metformin hydrochloride” currently on the principal display panel (PDP) to the side panel to reduce clutter on the PDP.

3. Ensure that the image of the tablet accurately represents the actual size, shape, color, and imprint of the commercial tablet and is not a schematic or computer-generated shape or image. In addition, this image should be less prominent and located away from important information such as proprietary name, established name and strength.

Kindly acknowledge receipt of this email.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA

Regulatory Project Manager,

CDER/OND

Office of Metabolism and Endocrinology Products

White Oak, (b) (6)

10903 New Hampshire Avenue,

Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
02/28/2014



NDA 204353

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

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

Dear Mr. Porter:

We acknowledge receipt on February 10, 2014, of your February 10, 2014, resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invokamet (canagliflozin and metformin hydrochloride) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We consider this a complete, class 2 response to our December 11, 2014, action letter. Therefore, the user fee goal date is August 10, 2014.

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/  
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ABOLADE ADEOLU  
02/19/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Thursday, January 30, 2014 8:55 AM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353

Dear Brandon,

Canagliflozin is recommended to be taken in the morning with the first meal of the day. Your fixed dose combination product will be recommended for twice daily use. Have you explored potential differences in the night-time occurrence of polyuria/nocturia, hypovolemia/hypotension and fall related adverse reactions depending on timing of administration in your overall canagliflozin program? If the data collected allows please compare or attempt to compare the nighttime occurrence of these product related adverse reactions when canagliflozin is administered as a full dose in the morning versus as a two half doses in the morning and evening and provide this information in your future resubmission.

Let me know if you have any further questions.

Regards,  
Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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ABOLADE ADEOLU  
01/30/2014



NDA 204353

**GENERAL ADVICE**

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

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for canagliflozin and metformin hydrochloride tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We acknowledge your January 3, 2014, submission, containing documentation for your Rationale for Non Inferiority Margin Selection, and Estimating the Relative Contributions of SGLT2 and SGLT1.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2013, and our agreement to respond to your proposed approach for the assessment between QD and BID dosing regimens.

We have reviewed the referenced material and have the following comments:

Your proposed assessment in the virtual trial setting is acceptable as a supportive evaluation of bridging between QD and BID dosing regimens of canagliflozin. Since the assessment is based on clinical trial simulations, it should not be regarded as a “non-inferiority” assessment. Our primary assessment will be based on the evaluation of outputs such as similarity of the time-course of predicted HbA1c responses for QD and BID dosing regimens.

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 (Acting)  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ERIC C COLMAN

01/24/2014

On behalf of Jean Marc Guettier



NDA 204353

**MEETING MINUTES**

Janssen Pharmaceuticals, Inc.  
c/o Janssen Research & Development, LLC  
Attention: Brandon D. 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 December 12, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invokamet (canagliflozin and metformin hydrochloride) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2013. The purpose of the meeting was to discuss your modeling and simulation plan.

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

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 (Acting)  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A

**Meeting Date and Time:** December 19, 2013 from 9:00 to 10:30 AM

**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 51, Conference Room: 1215  
Silver Spring, MD 20903

**Application Number:** NDA 204353  
**Product Name:** Invokamet (canagliflozin and metformin hydrochloride) tablets

**Indication:** Adjunct to diet and exercise to improve glycemic control in Adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

**Sponsor/Applicant Name:** Janssen Pharmaceuticals, Inc.

**Meeting Chair:** Jean-Marc Guettier, MD  
**Meeting Recorder:** Abolade (Bola) Adeolu

**FDA ATTENDEES**

Jean-Marc Guettier, MD- Director (Acting), Division of Metabolism & Endocrinology Products (DMEP)

Ali Mohamadi, MD- Clinical Team Lead

Hyon Kwon, PharmD- Clinical Reviewer, DMEP

Chandra Sahajwalla, PhD – Director, Division of Pharmacology 2 (DCPII), Office of Clinical Pharmacology (OCP)

Lokesh Jain, PhD - Clinical Pharmacology Lead, DCPII, OCP

Ritesh Jain, PhD – Clinical Pharmacology Reviewer, DCPII, OCP

Vikram Sinha, MD – Director, Division of Pharmacometrics, OCP

Nitin Mehrotra, PhD – Team Lead, Division of Pharmacometrics, OCP

Anshu Marathe, PhD- Pharmacometrics Reviewer, OCP

Thomas Permutt, PhD- Director, Division of Biometrics II (DBII)

Mark Rothmann, PhD – Lead Mathematical Statistician, (DBII)

Wei Liu, PhD- Statistical Reviewer, DBII

Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

**SPONSOR ATTENDEES**

### **Compound Development Team**

Kirk Ways, MD, PhD - Development Head Metabolism

Norman Rosenthal, MD - Vice President, Canagliflozin Compound Development Team Leader

### **Clinical Pharmacology, Translational Medicine, Pharmacogenomics, and Pharmacometrics**

Kenneth Turner, PhD - Clinical Pharmacology Therapeutic Area Head

Damayanthi Devineni, PhD - Director, Clinical Pharmacology Leader

Willem De Winter, PhD - Scientific Director, Model Based Drug Development

Jose Pinheiro, PhD – Senior Scientific Director, Model Based Drug Development

David Polidori, PhD - Head of Clinical and Translational Biomarkers, Cardiovascular and Metabolism

### **Clinical**

Rose (Rong) Qiu, MD, PhD – Study Physician

### **Biostatistics & Programming**

Surya Mohanty, PhD - Clinical Biostatistics Head

Gordon Law, PhD - Director, Statistical Leader

### **Global Regulatory Affairs**

Jacqueline Coelln-Hough, RPh - Sr. Director, Global Regulatory Affairs

Brandon Porter, MBA - Associate Director, Regulatory Affairs

## **1.0 BACKGROUND**

The applicant submitted a modeling and analysis plan to the Agency on November 6, 2013, followed by a meeting request on November 14, 2013. The meeting was granted and meeting preliminary comments were sent to the applicant on December 16, 2013.

## **2.0 DISCUSSION**

We are repeating below our comments from the letter containing the meeting preliminary comments, issued on December 16, 2013, followed by the Applicants response in underlined italics and meeting discussion and post-meeting comments in **bold** font.

1. Attachment 4 of your plan describes the possible impact, or lack thereof, of high inter-individual variability in absorption parameters on pharmacodynamic (PD) response. Please clarify if the PD effect that is simulated is of urinary glucose excretion. We recommend that you consider the following to demonstrate that the variability in Cmax has no meaningful effect on PD response:
  - a. Perform sensitivity analysis by predicting the profiles of the PD marker and HbA1c for a wide range of mean absorption parameters. The objective of the analysis should be to show that the worst case scenario of largest deviation from

the true PK profile in the absorption phase does not significantly affect the PD marker and HbA1c response. This simulation should account for the variability in EC50 as well.

- b. Calculate the prediction error near Tmax and at different time points along the PK profile for canagliflozin using the PK model. This will require generating predictions for a Phase 1/2 dataset with intensive PK sampling that was not used for model building. The current proposal does not provide sufficient assurance that you are able to predict the entire PK profile reasonably well and not just the C<sub>trough</sub>.

Applicant Response 1a: The PD effect that was simulated in Attachment 4 of the revised analysis plan used  $EC_{50} = 60\text{ng/ml}$ , which was based on the current estimate of EC50 for the effect of canagliflozin on HbA1c (not UGE).  $[PD\ effect = C(t)/(C(t)+EC_{50})]$

We propose to perform the requested sensitivity analyses over a range of absorption parameters covering the observed individual variability ( $k_a$ , 1 and 10 h<sup>-1</sup>;  $t_{lag}$ , 0.08 and 0.3 h). We propose including a range covering the endpoints of the 95% confidence interval of the estimated EC50.

Applicant Response 1b: The applicant proposed using data from Phase 1 study, DIA1032 as the external dataset. The study included 50 mg BID, 100 mg BID, 100 mg QD and 300 mg QD dose levels. PK profiles for these dose levels will be simulated for day 5 and will be compared against the observed data from this study

Does the Agency agree that an external evaluation using DIA1032 and the proposed sensitivity analysis can address comments #1a and 1b?

**Discussion:** The Agency agreed with the applicant's proposal to address comments 1a and 1b. The Agency recommended that the applicant calculate the prediction error near Tmax of the drug as an external evaluation using datasets from study DIA1032. The applicant also clarified that the inter-individual variability was not estimated on EC<sub>50</sub> due to limited concentration range in the studies.

2. We recommend that you use the full ordinary differential equation (ODE) dynamic model for all analyses and simulations. We acknowledge that the computation time will be longer with this approach compared to the method of averaging (MoA) approach. However, the MoA method assumes that QD and BID regimens will yield similar PD responses similar to the predictions for average steady state concentrations (C<sub>avg</sub>).

Applicant Response:

Summary

- For all practical purposes, MoA and Full ODE solutions are identical
- "Averaging" is a property of the equations arising from different time scales
  - Due to slow turnover of HbA1c relative to daily dosing

Proposal

- Use MoA for all model fitting and simulations

- Provide documentation confirming accuracy of MoA method
  - Final parameter estimates for MoA and Full ODE solutions
  - Simulated HbA1c profiles for a selected number of subjects

**Discussion:** The Agency agreed with applicant's proposal of using the MoA method.

3. Based on the equation 1 of the current model structure, it appears that an increase in drug concentration will result in an increase in the input to the HbA1c compartment. This will predict an increase in HbA1c rather than decrease. Please clarify.

Applicant Response: Emax is a negative number.

**Discussion:** The Agency accepted the applicant's clarification.

4. There appears to be a discrepancy in the scale of drug concentration in the goodness of fit plot (Figure 6, Observed versus Predicted) and the VPC plot (Figure 7). The concentrations range from 0-8 ng/ml in Figure 6, whereas the concentrations are as high as 1000 ng/ml in Figure 7. Please clarify.

Applicant Response: The data plotted in Figure 6 were the natural log of the concentrations (the axes were improperly labeled with the original units). A range of 0-8 on the log scale shown in Figure 6 corresponds to a range of 1-3000 ng/ml, consistent with the values in Figure 7.

**Discussion:** The Agency accepted the applicant's clarification.

5. You propose to estimate the individual baseline value of HbA1c. Have you considered fixing it to the value that was observed in the trial?

Applicant Response: We evaluated this option and we acknowledge that this can be done either way. We propose to estimate the individual baseline.

**Discussion:** The Agency accepted the applicant's approach of estimating baseline value of HbA1c.

6. Have you tried or considered the following alternative approach of parameterization for your model. Indirect response model 1 [ $dH/dt = k_{in} \cdot (1 - I_{max} \cdot C / (IC_{50} + C)) - k_{out} \cdot H$ ] where only the placebo data is used to estimate  $k_{out}$  and  $k_{in}$  is calculated as  $k_{in} = k_{out} \cdot H(0)$ . Since variability is observed in placebo response across trials, different  $k_{out}$  can be estimated for each study. Subsequently  $k_{out}$  can be fixed and  $I_{max}$  and  $IC_{50}$  can be estimated using data from treatment arms. Please comment.

Applicant response:

$$\text{Applicant: } \dot{H}(t) = -k_{out} H(t) + k_{out} \cdot \left( H(0) - \left( E_{max} \frac{C(t)}{C(t) + EC_{50}} + Ef_p \right) \cdot \frac{H(0) - 5}{8 - 5} \right)$$

$$\text{Agency: } \dot{H}(t) = -k_{out} H(t) + k_{out} \cdot \left( H(0) - I_{max} \frac{C(t)}{C(t) + IC_{50}} \cdot H(0) \right)$$

1. Scaling efficacy by either  $H(0)$ -5 or  $H(0)$

- Propose keeping  $H(0)$ -5 term as in Janssen proposal.
- Reflects observations that PG is unchanged in normoglycemic subjects

2. Single  $k_{out}$  and estimate  $Ef_p$  for each study or estimating separate  $k_{out}$  for each study

- $k_{out}$  is time constant for RBC turnover; not expected to vary between studies

**Discussion:** The Agency accepted applicant's proposed parameterization for the dynamic PK/PD model.

7. If the proposed additional parameter for 300 mg dose, i.e.,  $Ef_{300}$ , is significant, it is not clear what values of  $Ef_{300}$  will be used for simulating the 50 mg BID and 150 mg BID dosing regimen.

Applicant response: Because the  $Ef_{300}$  term is multiplied by an indicator function that is 0 for the 50 mg BID or 150mg BID regimens, it will not contribute to the efficacy for these regimens.

**Discussion:** The applicant clarified that the  $Ef_{300}$  term was not statistically significant. The Agency requested that the applicant submit information regarding the improvement in model predictions of HbA1c by including this parameter, even though it is not statistically significant.

8. We will be discussing your proposed non-inferiority virtual trial simulation with our statistical colleagues and are unable to comment on it at this stage.

**Discussion:** The plan was discussed briefly and the Agency reiterated that any comments on the design of non-inferiority virtual trial simulation will be communicated to the applicant after an internal meeting with statistics and clinical.

**Additional discussion:**

1. The applicant presented additional clinical data estimating the magnitude of gut effect for 300 mg dose vs. the 100 mg dose of canagliflozin. The Agency recommended that the data from DIA1045 and other relevant information for estimating the magnitude of gut effect should be included in the package at the time of NDA submission.
2. The Agency recommended that the applicant should submit all relevant datasets and program codes at the time of NDA submission.

#### 4.0 ISSUES REQUIRING FURTHER DISCUSSION

Approach for assessment of non-inferiority between QD and BID dosing regimen

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/s/  
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JEAN-MARC P GUETTIER  
01/15/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Friday, January 10, 2014 10:23 AM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353 (cana-met): safety update for proposed resubmission

Dear Brandon,

Your overall proposal for updating clinical safety data is reasonable. In addition, we request that you submit narratives for subjects who died, had malignancy of interest (i.e., pheochromocytomas, Leydig cell tumors, renal cell carcinoma), fatal or hemorrhagic/necrotizing pancreatitis, or severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome) since the 4-Month Safety Update submitted on April 5, 2013. Also, if new or unexpected safety concerns arise from the NDA resubmission, we may request more summaries, narratives, or unblinded data.

Kindly acknowledge receipt of this email and let me know if you have any further comments.

Regards,  
Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
01/10/2014



NDA 204353

**DEFICIENCIES PRECLUDE DISCUSSION**

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

Dear Mr. Porter:

Please refer to your December 12, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for canagliflozin and metformin hydrochloride immediate release tablets, 50/500mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to our February 16, 2013, letter in which we notified you of our target date of November 14, 2013, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

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/  
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ABOLADE ADEOLU  
11/06/2013

**PeRC PREA Subcommittee Meeting Minutes  
October 23, 2013**

**PeRC Members Attending:**

Lynne Yao  
Hari Cheryl Sachs  
Karen Davis-Bruno  
Rosemary Addy  
Patricia Dinndorf  
Tom Smith  
Shrikant Pagay  
Ethan Hausman  
William J. Rodriguez  
Peter Starke  
Daiva Shetty  
Colleen LoCicero  
Martha Nguyen  
Dianne Murphy  
Susan McCune  
Gergory Reaman  
Dionna Green  
Michelle Roth-Cline  
Renan Bonnel  
George Greeley  
Jane Inglese

**Guests Attending:**

Maura Oleary (CBER)	Jessica Lee (DPARP)
Kathy Robie Suh (DHP)	Sarah Yim (DPARP)
George Shashaty (DDDP)	Hyon Kwon (DMEP)
David Kettl (DHP)	Michelle Jordan Garner (DPARP)
Nichella Simms (PMHS)	
Courtney Suggs (OCP)	
Donna Snyder (PMHS)	
Milena Lolic (DDDP)	
Lawren Slate (OCP)	
Colleen Tholen (ONDQA)	
Janet Maynard (DPARP)	
Nikolay Nikolov (DPARP)	
Satjit Brar (OCP)	
Carol Kasten (PMHS)	
Milgna Lolic	
J. Paul Phillips (DDDP)	
Jayabharathi Vaidyanathan (OCP)	
Ali Mohamadi (DMEP)	
Juli Tomaino (DGIEP)	

**Agenda**

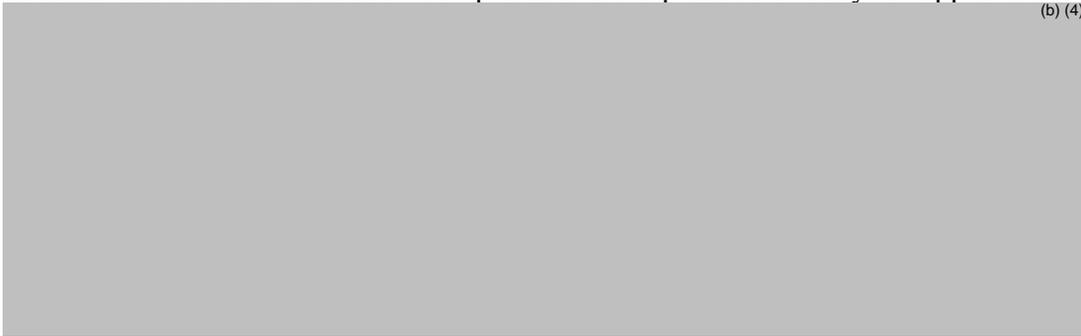
10:00 NDA 204353 Invokamet (canagliflozin/metformin) Partial Waiver/Deferral/Plan

(b) (4)

**Invokamet (canagliflozin/metformin) Partial Waiver/Deferral/Plan**

- NDA 204353 seeks marketing approval for Invokamet (canagliflozin/metformin) for the treatment of type 2 diabetes mellitus.
- The application was submitted on December 12, 2012, and has a PDUFA goal date of December 12, 2013.
- The application triggers PREA as directed to a new active ingredient.
- A waiver is being requested for pediatric patients aged birth to less than ten years because studies are impossible or highly impractical.
- *Division justification for waiver:* Epidemiologic data reveal that there are few patients less than 10 years of age with type 2 diabetes mellitus. This age cut-off for studies is consistent with other products recently approved for the treatment of type 2 diabetes mellitus such as linagliptin, alogliptin, and liraglutide.
- A deferral is being requested for pediatric patients aged 10 to less than 18 years because adult studies have been completed and the product is ready for approval.

(b) (4)



- Phase 3 study: A 26-week randomized, double-blind, placebo-controlled, parallel group, multi-center study, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy, safety, and tolerability of canagliflozin in (b) (4) (10 and <18 years of age) with T2DM, as add-on to metformin and as monotherapy (b) (4)

(b) (4)

Protocol Submission: 12/31/2015

Study Completion: 6/30/2020

Study Submission: 12/31/2020

- The same studies are planned for canagliflozin to comply with PREA. The canagliflozin deferral and plan was agreed to by the PeRC on February 13, 2013.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to less than 10 years because studies are impossible or highly

impractical. This age cut off for a waiver has been accepted for all products to treat T2DM to date.

- The PeRC agreed with the Division to grant a deferral for pediatric patients aged 10 to less than 18 years because the product is ready for approval in adults. The PeRC agreed to the proposed study design and timelines for the deferred studies.

(b) (4)



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/s/  
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JANE E INGLESE  
11/05/2013

## Adeolu, Abolade

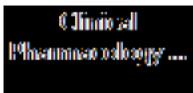
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**From:** Adeolu, Abolade  
**Sent:** Wednesday, October 30, 2013 1:16 PM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com); Saran, Sukhdev [JRDUS] (SSaran@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353

Dear Brandon,

Attached are our responses to your questions regarding your analysis plan submitted October 15, 2013.

Thanks, Bola



Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

**Clinical Pharmacology comments**

Question 1:

Does the Agency concur with the overall proposal for the analysis plan?

**FDA Response:** No, we do not agree with your modeling plan to bridge the efficacy of QD and BID regimen for the following reasons:

I.

II.

III.

IV.

V.

(b) (4)

Although, in principle, the modeling approach is feasible but due to the limitations of the available data and the proposed analysis approach as outlined above, we do not believe the current proposal would be adequate to bridge the efficacy of QD and BID dosing regimens.

Question 2:

[REDACTED] (b) (4)

**FDA Response:** See response to question 1. The issues mentioned in question 1 should be resolved first.

Question 3:

As described in the analysis plan, the Sponsor proposes performing dynamic, integrated population PK/PD model-based analyses to support the bridging from QD to BID using a PK/PD model developed specifically in subjects on background metformin therapy [REDACTED] (b) (4)

[REDACTED]

[REDACTED] Does the Agency agree with this approach?

**FDA Response:** See response to question 1. The issues mentioned in question 1 should be resolved first.

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/s/  
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ABOLADE ADEOLU  
10/30/2013



NDA 204353

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Janssen Pharmaceuticals, Inc.  
c/o Janssen Research & Development, LLC  
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 December 12, 2012, received December 12, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Canagliflozin and Metformin Hydrochloride Tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to your April 30, 2013, correspondence, received April 30, 2013, requesting review of your proposed proprietary name, Invokamet. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Invokamet, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 12 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Abolade (Bola) Adeolu at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, 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/  
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CAROL A HOLQUIST  
07/26/2013



NDA 204353

**INFORMATION REQUEST**

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

Dear Mr. Porter:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the low, nominal, and high percent of acetonitrile used in your Robustness studies for the validation of the assay method of metformin HCl in your drug product.
2. Provide, also, the low, nominal, and high concentration of dihydrogen phosphate buffer solutions used in the Robustness studies for the assay method of metformin HCl in your drug product
3. Provide information, including quantitative details, for the preparation of the stock solutions containing placebo and API at 100% level, used for the validation of the accuracy of the method of determining (b) (4) in your canagliflozin/metformin HCl tablets.
4. State whether the % purity of your (b) (4) reference standard was employed in the construction of your log-log calibration curve. In addition, provide the % purity of the (b) (4) that was used to construct this calibration curve and the % purity of this compound used in the preparation of the stock solutions, in your validation/accuracy studies for the determination of this impurity.
5. In the accuracy section of the validation of the determination of (b) (4) in the tablets, you stated that each concentration of (b) (4) will be prepared three times by serial dilutions of three separately prepared stock solutions. Thus, one would anticipate three % recovery values at the 750 ng/mL concentration. However, only one result is listed for the 750 ng/mL concentration. Explain this apparent discrepancy.
6. In your validation-specificity-studies, explain how you determined that metformin HCl does not interfere with the analytical method for the dissolution of canagliflozin in your

tablets, and why, conversely, canagliflozin does not interfere with the dissolution related analysis of metformin HCl.

7. Explain why at least 14 out of 72 batches of drug product in your registration stability program gave [REDACTED]<sup>(b) (4)</sup>, time points.
8. For every NDC # that is listed in your HOW SUPPLIED section of the package insert, SPL labeling, and/or container labels, provide the corresponding bottle size in the Container Closure section of your NDA. In addition, clarify whether there are any bottles (e.g., the [REDACTED]<sup>(b) (4)</sup> container) listed in your Table 1 (Intended Commercial Packaging Configurations for the Drug Product) that do not show an NDC # in your NDA.

If so, provide the NDC numbers, the purpose of the bottles, and the tablet count for each strength of the drug product.

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

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

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/s/  
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DANAE D CHRISTODOULOU  
06/28/2013

**From:** Adeolu, Abolade  
**Sent:** Thursday, June 13, 2013 8:17 AM  
**To:** Porter, Brandon [JRDUS]  
**Cc:** Saran, Sukhdev [JRDUS]; Adeolu, Abolade  
**Subject:** RE: NDA 204353 (canagliflozin+metformin FDC) / Scheduling Post Mid-Cycle Meeting Call

Good morning Brandon,

We would like narratives for those events that were listed in the 4-Month Safety Update but for which no narratives were provided previously (meaning we only need narratives for new events since canagliflozin NDA).

For events that were previously submitted under canagliflozin NDA, also submit updated narratives if there are any (please separate updated narratives from new narratives).

Thanks,

**Bola Adeolu**  
**301 796-4264**

**From:** Porter, Brandon [JRDUS] [<mailto:BPorter3@its.jnj.com>]  
**Sent:** Wednesday, June 12, 2013 1:59 PM  
**To:** Adeolu, Abolade  
**Cc:** Saran, Sukhdev [JRDUS]  
**Subject:** RE: NDA 204353 (canagliflozin+metformin FDC) / Scheduling Post Mid-Cycle Meeting Call

Hi Bola, just following up on the clarification request below.

Many thanks for your help.

Best,  
Brandon

**From:** Porter, Brandon [JRDUS]  
**Sent:** Friday, June 07, 2013 10:38 AM  
**To:** 'Adeolu, Abolade'  
**Cc:** Saran, Sukhdev [JRDUS]  
**Subject:** RE: NDA 204353 (canagliflozin+metformin FDC) / Scheduling Post Mid-Cycle Meeting Call

Hi Bola,

As we were preparing our responses to the information requests from the Mid Cycle Communication letter, a question came up regarding the clinical request:

“1. Provide narratives for any additional subject with adjudicated hepatic events, bladder, breast, and renal cancer events as of the 4-Month Safety Update.”

It is unclear to us what is meant by “as of the 4-Month Safety Update”. Is the Agency requesting:

- A. Narratives ONLY for events that were already listed in the 4-Month Safety Update (event cutoff date of 31 Dec 2012) but for which no narratives were provided; or
- B. Narratives for events that occurred AFTER the 31 Dec 2012 cutoff of the 4-Month Safety Update; or
- C. Both of the above.

Also, if the answer is B or C, what is the cutoff date that the Agency had in mind for new narratives?

Many thanks for your help clarifying this request.

Best,  
Brandon

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ABOLADE ADEOLU  
06/17/2013



NDA 204353

**MID-CYCLE COMMUNICATION**

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

Dear Mr. Porter:

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

We also refer to the teleconference between representatives of your firm and the FDA on May 29, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** May 29, 2013

**Application Number:** NDA 204353

**Product Name:** canagliflozin and metformin hydrochloride tablets

**Indication:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

**Applicant Name:** Janssen Pharmaceuticals, Inc.

**Meeting Chair:** Jean-Marc Guettier, MD

**Meeting Recorder:** Abolade (Bola) Adeolu

**FDA ATTENDEES**

Jean-Marc Guettier, MD- Clinical Team Lead, Division of Metabolism & Endocrinology Products (DMEP)

Hyon Kwon, PharmD- Clinical Reviewer, DMEP

Todd Bourcier, PhD - Nonclinical Supervisor, DMEP

Fred Alavi, PhD - Nonclinical Reviewer, DMEP

Lokesh Jain, PhD - Clinical Pharmacology Team Lead, Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Todd Sahlroot, PhD - Deputy Director, Division of Biometrics II (DBII)

Wei Liu, PhD- Statistical Reviewer, DBII

Ali Niak, MD- Medical Officer, Office of Surveillance & Epidemiology (OSE), Division of Pharmacovigilance I (DPVI)

Christine Chamberlain, PharmD, BCPS, CDE- Safety Evaluator, OSE, DPVI

Christian Hampp, PhD- Senior Staff Fellow, OSE, Division of Epidemiology I

Cynthia LaCivita, PharmD- Drug Risk Management Analyst, Team Leader, OSE

Steven Hertz, MS, MBA- Consumer Safety Officer, Office of Compliance

Kimberly Taylor, MPH, MBA- Strategic Programs

Patrick Zhou- Independent Assessor, Eastern Research Group Attendees

Julie Marchick, MPH - Chief, Project Management Staff

Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

## **APPLICANT ATTENDEES**

Kirk Ways, MD, PhD- Development Head Metabolism  
Hamish Ross, PhD- Vice President, Clinical Research, Compound Development Team Leader  
Yinka Williams, PhD- Senior Director, CMC Leader  
Lisa Lumia, PhD- Director, CMC Regulatory Affairs  
Rose (Rong) Qiu, MD PhD- Study Physician  
Kenneth Turner, PhD- Clinical Pharmacology Therapeutic Area Head  
Damayanthi Devineni, PhD- Director Clinical Pharmacology Leader  
Surya Mohanty, PhD- Clinical Biostatistics Head  
Jaya Natarajan, PhD- Director, Biostatistics  
Gordon Law, PhD- Director, Statistical Leader  
Jacqueline Coelln-Hough, RPh- Senior Director, Global Regulatory Affairs  
Sukhdev Saran, MBA- Director, Global Regulatory Affairs  
Brandon Porter, JD, MBA- Associate Director, Global Regulatory Affairs  
Jeffy John- Senior Associate, Regulatory Affairs

## **1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## **2.0 SIGNIFICANT ISSUES**

### **Clinical and Statistics**

The magnitude of HbA1c reduction in Study DIA2003 where canagliflozin doses were administered twice daily (i.e., BID) was smaller than that observed in Study DIA3006 where the same doses of canagliflozin were administered once-daily (i.e., QD). We note that you used a bootstrap method to bridge the QD dosing in Study DIA3006 to the BID dosing regimen in Study DIA2003. We have several reservations. Your analysis is post-hoc, and as such is subject to the usual limitations of analyses conducted with data in-hand. Secondly, cross-trial comparisons are difficult to interpret. Finally, your method uses the observed baselines in the two studies to reconcile between-study differences in HbA1c. While HbA1c baseline differences represent an important aspect of the two studies, there may be many other factors that also influence HbA1c.

### **Clinical pharmacology**

If the exposure-response relationship for plasma canagliflozin concentrations and HbA1C response is not well supported, the efficacy/safety data from the once-daily dosing regimen of canagliflozin cannot be bridged to the proposed twice-daily dosing regimen for the fixed dose combination (FDC) based on demonstration of PK equivalence.

#### **Post-meeting Note:**

During the teleconference you referred to updated exposure-response analyses incorporating data from additional Phase 3 trials. You should note that submission of this pivotal data not provided in the original application would likely trigger an extension of the review clock.

### **3.0 INFORMATION REQUESTS**

#### **Clinical**

1. Provide narratives for any additional subject with adjudicated hepatic events, bladder, breast, and renal cancer events as of the 4-Month Safety Update.

#### **Chemistry Manufacturing and Controls**

2. Update your specifications for the canagliflozin drug substance to include an acceptance criterion (limit) for (b) (4) and refer to a validated method for the determination of this genotoxic impurity. The maximum level of this impurity should be the same as that which was approved in the drug substance specification for NDA 204042 (Invokana, Canagliflozin Tablets). Thus, the acceptance level for (b) (4) should be no more than (b) (4) ppm.
3. In your tables for the “Theoretical Quantitative Ingredient Statement per Batch” for the metformin HCl and hypromellose (b) (4), provide the theoretical amounts of metformin HCl and hypromellose that are actually added to these (b) (4), since not all of the amounts of these ingredients, listed in the tables, are added to the (b) (4). Similarly, provide the theoretical amount of (b) (4) Yellow that is applied during the coating process in the batch formulae for the tablets.
4. State whether or not you will carry out any reprocessing steps for the manufacture of the drug product, and if so, describe these steps.
5. Since the acceptance criteria for (b) (4) is based on a unit amount of the canagliflozin drug substance in the drug product, the maximum level of this impurity should be the same as that which was approved in the drug product specification for NDA 204042 (Invokana, Canagliflozin Tablets). Thus, the acceptance level for (b) (4) - (b) (4) should be no more than (b) (4) ppm in all strengths of the drug product. Moreover, all of your stability data at 5°C, 25°C/60% RH, 30°C/75% RH and 40°C/75% RH from the proposed-to-be-marketed product with desiccant, support the (b) (4) ppm level.

6. Provide the source and a Certificate of Analysis (CoA) for the Impurity (b) (4) that is used in your Selectivity Solution for the assay of metformin HCl and its impurities in your canagliflozin/metformin HCl tablets. If Impurity (b) (4) is prepared “in house”, also briefly describe its synthesis and proof of structure.
7. Provide the batch number and a CoA for your “Selectivity Batch” of (b) (4) which is employed to prepare the “Selectivity Solution”, used for the determination of the canagliflozin assay and canagliflozin impurity levels in your drug product.
8. Provide the protocol for qualifying in the future a reference standard for metformin HCl.
9. Provide engineering drawings, with appropriate dimensions for your (b) (4) bottles and their accompanying (b) (4).
10. Provide stability data from later time points that were originally submitted, from samples that were packaged with and without desiccant, to support your proposed expiry of the drug product.
11. Provide the bracketing design, based on product container, for your proposed to be marketed product in your post-approval stability protocol.

### **Biopharmaceutics**

12. In Module 2, section 2.7.1, Appendix 3.2 (page 81), you have tabulated the mean % dissolved (range) for both API components of the proposed FDC Tablets. Dissolution data for Lot # 1HG5153-X for both canagliflozin and metformin do not match the data for the same lot presented in module 3, section 3.2.P.5.6, Tables 17 and 18 (pages 29, 30). Check the data of the other lots and clarify which data sets are correct and which ones are wrong.
13. In your response to FDA Communication dated Feb 16, 2013, you submitted individual vessel dissolution data for the FDC tablet batches that were used to establish the acceptance criteria for both API components (Tables 58 – 81). The mean data and particularly the ranges at each time point do not seem to match those in the original submission for most of the batches. Explain the differences in numerical values between these individual data sets and the Tables referred to in Comment 1 above. Clarify if some of the data sets are at T<sub>0</sub> or some other stability time point.
14. In Dissolution Validation Reports DISS-37, DISS-41 and DISS-38 for 50 mg canagliflozin, 150 mg canagliflozin and metformin, respectively, section 2.5 summarizes the Robustness of dissolution and chromatographic assay parameters. You conclude that the dissolution and assay methods are robust based on the data generated by deliberately making small changes to the parameters. The data are neither presented nor referenced in a different section or subsection of the NDA. Provide the experimental data that support robustness of the methods.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

None to report at this time

**5.0 ADVISORY COMMITTEE MEETING**

None anticipated

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

Wrap-Up meeting: November 7, 2013

Late-Cycle meeting: September 12, 2013 12:00 to 1:00 PM

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/s/  
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ABOLADE ADEOLU  
06/06/2013



NDA 204353

**FILING COMMUNICATION**

Janssen Pharmaceuticals, Inc.  
c/o Janssen Research & Development, LLC  
Attention: Brandon D. 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 December 12, 2012, received December 12, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for canagliflozin and metformin hydrochloride immediate release tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to your amendment dated January 18, 2013, containing updated email addresses for your administrative contacts.

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is **December 12, 2013**.

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 post-marketing commitment requests by **November 14, 2013**. In addition, the planned date for our internal mid-cycle review meeting is **May 14, 2013**. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issue:

#### Clinical Pharmacology

You have indicated that the tablet formulations used in the study DIA2003, entitled “A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy” are linked to the to-be marketed canagliflozin and metformin hydrochloride immediate release fixed dose combination (CANA/MET IR FDC) tablets through the pharmacokinetic bioequivalence between twice-daily and once-daily administered tablets assessed in the study DIA1032, entitled “An Open-Label, Multiple-Dose Study to Assess the Steady-State Pharmacokinetics, Pharmacodynamics and Safety of Once-Daily Versus Twice-Daily Dosing With Canagliflozin in Healthy Subjects”. Adequacy of this bridging strategy will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

#### Biopharmaceutics

1. Please provide a Dissolution Method Development Report including rationale for each of the three dissolution method conditions you have proposed in your NDA. Due to differences in dissolution media for the canagliflozin component of the fixed-dose combination (FDC) tablet compared to the proposed single-entity product in NDA 204042, justification for development of the methods cannot be referenced to development parameters of the latter.

Your dissolution development report should include the following:

- a. Solubility data already generated for the drug substances.
- b. Detailed description of the dissolution tests being proposed for the evaluation of your FDC product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution methods as the optimal tests for your product. Include data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. We recommend use of at least twelve samples per testing variable.
- c. Provide the complete dissolution profile data (*individual value, mean, n, SD, profiles*) for each entity.

- d. Data to support the discriminating ability of the selected methods. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution methods should compare the dissolution profiles of the proposed product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm 10\text{-}20\%$  change to the specification- ranges of these variables). In addition to (b) (4) reported in the NDA, present results of investigation of other critical manufacturing variables on the discriminating power of the dissolution methods.
2. Provide the rationale for selecting a rotation speed of 75 rpm for the dissolution testing of the canagliflozin component in the dissolution method development report. Provide dissolution data at 50 rpm.
3. Identify the FDC tablet lots/batches that were selected for setting the proposed dissolution acceptance criteria, including the lot numbers, the clinical studies in which they were used, and if they were registration batches on stability. Provide the complete dissolution data for the identified lots (*individual, mean, n, SD, profile*).
4. Provide the complete dissolution profile data (i.e., 15, 20, 30, 45, and 60 minutes,  $n=12$ ) for the bio-batches (clinical & PK) and primary (registration) stability batches (*individual and mean values*). If these are already provided in the NDA, please provide module and section numbers.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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 patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, 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 of pediatric studies in children 0 to less than 10 years of age, for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies in older children and adolescents  $\geq 10$  to  $< 18$  years of age, for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

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

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, MD  
Director  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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MARY H PARKS  
02/16/2013



NDA 204353

**MEETING PRELIMINARY COMMENTS**

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

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invokamet (canagliflozin and metformin hydrochloride) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to your November 14, 2013, correspondence, received November 15, 2013, requesting a meeting to discuss your modeling and simulation analysis plan.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** Type A

**Meeting Date and Time:** December 19, 2013 9:00 to 10:30 AM

**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 51, Conference Room: 1215  
Silver Spring, MD 20903

**Application Number:** NDA 204353

**Product Name:** Invokamet (canagliflozin and metformin hydrochloride) tablets

**Indication:** Adjunct to diet and exercise to improve glycemic control in Adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

**Sponsor/Applicant Name:** Janssen Pharmaceuticals, Inc.

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 19, 2013, between Applicant and the Division of Metabolism & endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## 1. BACKGROUND

NDA 204353 for Invokamet (canagliflozin and metformin hydrochloride) tablets was received on December 12, 2012. A complete response letter was issued on December 12, 2013.

The purpose of this meeting is to discuss the modeling and simulation analysis plan to bridge the daily dosing canagliflozin regimen with the twice daily dosing regimen of the canagliflozin and metformin immediate release fixed dose combination.

## 2. DISCUSSION

We have reviewed your revised modeling plan to bridge the QD and BID dosing regimens for canagliflozin and have some comments, which are outlined below. We would like you to provide clarification for these comments during the planned meeting on December 19, 2013. We view the December 19, 2013, meeting as an opportunity for a two-way dialogue on the specifics of your modeling plan and encourage you to present the details of your plan in a step-wise manner (including the details on input parameters, parameter uncertainty, and estimates of variability). Please note that we will not be able to comment on the acceptability of specific components during this meeting; instead, we will convey our final decision on the acceptability of your proposal in a follow-up communication. Whether the results from the agreed upon modeling and simulation plan will adequately demonstrate bridging between QD and BID dosing regimen of canagliflozin will be a review issue.

### **Clinical Pharmacology comments on the modeling and simulation plan submitted on November 14, 2013:**

1. Attachment 4 of your plan describes the possible impact, or lack thereof, of high inter-individual variability in absorption parameters on pharmacodynamic (PD) response. Please clarify if the PD effect that is simulated is of urinary glucose excretion. We recommend that you consider the following to demonstrate that the variability in C<sub>max</sub> has no meaningful effect on PD response:
  - a. Perform sensitivity analysis by predicting the profiles of the PD marker and HbA1c for a wide range of mean absorption parameters. The objective of the analysis should be to show that the worst case scenario of largest deviation from the true PK profile in the absorption phase does not significantly affect the PD marker and HbA1c response. This simulation should account for the variability in EC<sub>50</sub> as well.
  - b. Calculate the prediction error near T<sub>max</sub> and at different time points along the PK profile for canagliflozin using the PK model. This will require generating predictions for a Phase 1/2 dataset with intensive PK sampling that was not used for model building. The current proposal does not provide sufficient assurance

that you are able to predict the entire PK profile reasonably well and not just the  $C_{\text{trough}}$ .

2. We recommend that you use the full ordinary differential equation (ODE) dynamic model for all analyses and simulations. We acknowledge that the computation time will be longer with this approach compared to the method of averaging (MoA) approach. However, the MoA method assumes that QD and BID regimens will yield similar PD responses similar to the predictions for average steady state concentrations ( $C_{\text{avg}}$ ).
3. Based on the equation 1 of the current model structure, it appears that an increase in drug concentration will result in an increase in the input to the HbA1c compartment. This will predict an increase in HbA1c rather than decrease. Please clarify.
4. There appears to be a discrepancy in the scale of drug concentration in the goodness of fit plot (Figure 6, Observed versus Predicted) and the VPC plot (Figure 7). The concentrations range from 0-8 ng/ml in Figure 6, whereas the concentrations are as high as 1000 ng/ml in Figure 7. Please clarify.
5. You propose to estimate the individual baseline value of HbA1c. Have you considered fixing it to the value that was observed in the trial?
6. Have you tried or considered the following alternative approach of parameterization for your model. Indirect response model 1 [ $dH/dt = k_{in} * (1 - I_{max} * C / (IC_{50} + C)) - k_{out} * H$ ] where only the placebo data is used to estimate  $k_{out}$  and  $k_{in}$  is calculated as  $k_{in} = k_{out} * H(0)$ . Since variability is observed in placebo response across trials, different  $k_{out}$  can be estimated for each study. Subsequently  $k_{out}$  can be fixed and  $I_{max}$  and  $IC_{50}$  can be estimated using data from treatment arms. Please comment.
7. If the proposed additional parameter for 300 mg dose, i.e.,  $Ef_{300}$ , is significant, it is not clear what values of  $Ef_{300}$  will be used for simulating the 50 mg BID and 150 mg BID dosing regimen.
8. We will be discussing your proposed non-inferiority virtual trial simulation with our statistical colleagues and are unable to comment on it at this stage.

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/s/  
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ABOLADE ADEOLU  
12/16/2013



NDA 204353

**MEETING REQUEST GRANTED**

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

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for r Invokamet (canagliflozin and metformin hydrochloride) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to your November 14, 2013, correspondence requesting a meeting to discuss your modeling and simulation analysis plan. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

**Date:** December 19, 2013

**Time:** 9:00 to 10:30 AM

**Location:** 10903 New Hampshire Avenue  
White Oak Building 51, Conference Room: 1215  
Silver Spring, Maryland 20903

**Invited CDER Participants:**

Jean-Marc Guettier, MD- Director (Acting), Division of Metabolism & Endocrinology  
Products (DMEP)

Ali Mohamadi, MD- Clinical Team Leader (Acting), DMEP

Hyon Kwon, PharmD- Clinical Reviewer, DMEP

Chandra Sahajwalla, PhD – Director, Division of Pharmacology 2 (DCPII), Office of Clinical  
Pharmacology (OCP)

Lokesh Jain, PhD - Clinical Pharmacology Team Lead, DCPII, OCP

Ritesh Jain, PhD – Clinical Pharmacology Reviewer, DCPII, OCP

Vikram Sinha, MD – Director, Division of Pharmacometrics, OCP

Nitin Mehrotra, PhD – Pharmacometrics Team Leader, Division of Pharmacometrics, OCP

Anshu Marathe, PhD – Pharmcometrics Reviewer, Division of Pharmacometrics, OCP

Mark Rothmann, PhD – Lead Mathematical Statistician, Division of Biometrics II (DBII)

Wei Liu, PhD- Statistical Reviewer, DBII

Julie Van der Waag, MPH - Chief, Project Management Staff

Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

Please e-mail me any updates to your attendees at Abolade.Adeolu@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Abolade (Bola) Adeolu at (301) 796-4264.

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

Enclosure:

Foreign Visitor Data Request form

**FOREIGN VISITOR DATA REQUEST FORM**

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITIZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	December 19, 2013 9:00 AM
MEETING ENDING DATE AND TIME	December 19, 2013 10:30 AM
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	10903 New Hampshire Avenue White Oak Building 51, Conference Room: 1215 Silver Spring, Maryland 20903
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Abolade (Bola) Adeolu Regulatory Project Manager [REDACTED] (b) (6) (301) 796-4264
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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ABOLADE ADEOLU  
11/18/2013

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Tuesday, November 12, 2013 9:31 AM  
**To:** Porter, Brandon [JRDUS] (BPorter3@its.jnj.com); Saran, Sukhdev [JRDUS] (SSaran@its.jnj.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 204353(cana-met)

Dear Brandon,

Thank you for submitting the revised modeling plan.

We would like to inform you that the plan submitted cannot be reviewed within this review cycle. The approach of using modeling and simulation to bridge efficacy of QD and BID dosing regimen is feasible and we can discuss this approach further.

We believe that a face to face meeting, as proposed by you, will be useful for us to completely understand and discuss your approach. However, it will not be feasible for us to hold this meeting before the week of December 15th. If such a meeting is held in future, we would like you to present your modeling and simulation plan in a step-wise manner for us to understand it better. We will be sending comments on your revised modeling plan ahead of the meeting.

Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, (b) (6)  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
11/13/2013



IND 110545

**MEETING REQUEST -  
Written Responses**

Janssen Research & Development, L.L.C  
Attention: Brandon D. Porter  
Global Regulatory Affairs  
3210 Merryfield Row  
San Diego, CA 92121

Dear Mr. Porter:

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/metformin) immediate-release fixed-dose combination tablet.

We also refer to our May 8, 2012, communication notifying you that we would provide a written response to the questions in your April 25, 2012, meeting request after receiving your background materials. The background materials were received on June 5, 2012.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, call Jena Weber at (301) 796-1306.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

Your questions are repeated below and our responses follow in bold font.

**Chemistry, Manufacturing & Controls (CMC)**

**Question 1:** The canagliflozin drug substance used in the manufacture of the CANA/MET IR FDC tablets is the same drug substance used in the manufacture of canagliflozin tablets (NDA 204-042). The Sponsor plans to cross-reference the canagliflozin tablet NDA (204-042) for all canagliflozin drug substance information. Does the Agency agree with this approach?

**FDA Response: It is acceptable to cross-reference the canagliflozin tablet NDA (204042) for all canagliflozin drug substance information.**

**Question 2:** The Sponsor plans to submit one executed batch record from a single representative batch of each tablet strength (50/500, 150/500, 50/1,000 and 150/1,000 mg) of CANA/MET IR FDC tablets manufactured to support the primary stability studies. Does the Agency agree with this approach?

**FDA Response: Your plan for submitting the executed batch records is acceptable.**

**Question 3:** Does the Agency agree with the proposal to provide 9 months of drug product registration stability data on all batches in the proposed commercial packaging configuration(s) in the CANA/MET IR FDC NDA (204-353) with the additional 3 months of data (for a total of 12 months) to be provided within 4 months after the NDA submission date?

**FDA Response: No, we do not agree with your proposed submission of 9 months of stability data in the NDA followed by a stability update. A minimum of 12-month long-term and 6-month accelerated stability data package should be included in the initial NDA submission in order for us to determine a realistic expiry for marketing the product. In accordance with Good Review Management Principles and Practices (GRMPs) timelines, a complete NDA should be submitted for filing, and we cannot guarantee that we will review unsolicited amendments.**

**Question 4:** The Sponsor plans to submit a post approval change (b) (4)

Does the Agency agree with the Sponsor's plans to submit this change as outlined in this submission?

**FDA Response: You may** (b) (4)

## Non-Clinical

**Question 5:** The Sponsor proposes referring to the nonclinical information in the canagliflozin tablet NDA (204-042) (and corresponding 4MSU); no new data is anticipated for the CANA/MET IR FDC NDA (204-353). Does the Agency agree with this approach?

**FDA Response:** We agree with your proposal; however, we ask that you include the 3-month rat combination toxicology and Segment-II rat combination study reports in the FDC NDA.

## Clinical Pharmacology

**Question 6:** The Sponsor proposes referring to the clinical pharmacology and biopharmaceutical information in the canagliflozin tablet NDA (204-042) (and corresponding 4MSU) and only submitting new clinical pharmacology and biopharmaceutical information to the CANA/MET IR FDC NDA (204-353) consisting of an updated Summary of Biopharmaceutics Module 2.7.1 and study reports for the new Phase 1 studies. Does the Agency agree with this approach?

**FDA Response:** We agree with this proposal.

## Clinical

**Question 7:** The Sponsor proposes referring to the clinical information in the canagliflozin tablet NDA (204-042) (and corresponding 4MSU) and only submitting new clinical information to the CANA/MET IR FDC NDA (204-353) (new Module 2 Clinical Overview and Clinical Summaries, and new study report for the one Phase 2 safety and efficacy study [DIA2003]). Does the Agency agree with this approach?

**FDA Response:** You should include summaries and discussions relevant to the efficacy and safety of the combination therapy of canagliflozin plus metformin. Complete study reports of any individual studies, not previously submitted to the canagliflozin NDA (204042), that support marketing of the fixed-dose combination product should be included. Your plan to cross-reference clinical information that is already presented in the canagliflozin NDA (204042) is acceptable. To facilitate review, please include electronic hyperlinks to cross-referenced data.

**In the safety summary of the CANA/MET IR FDC NDA, provide a summary and dataset from pooled Phase 3 placebo-controlled studies where canagliflozin was used as add-on therapy to metformin (e.g., DIA3006 [exclude sitagliptin treatment arm], DIA3002, and DIA3012). Present safety data according to the following treatment arms: all canagliflozin, canagliflozin 100 mg, canagliflozin 300 mg, and placebo. The safety analyses for this pool should include all of the major classes of adverse events (i.e., deaths, serious adverse events, discontinuations due to adverse events, common adverse events, and all adverse events of interest) as well as laboratory and vital sign data. Summarize these analyses in Module 2 and in the Integrated Summary of Safety and highlight differences, if**

any, in this subgroup from the overall pool of placebo controlled trial in the canagliflozin NDA (i.e., Safety Dataset 1).

Please submit narratives for cases of deaths, serious adverse events, discontinuations due to adverse events, and adverse events of interest for studies not included in the canagliflozin NDA (204042).

## Regulatory

**Question 8:** The Sponsor proposes to submit financial disclosure information only for the clinical investigators involved in the new clinical studies to be included in the CANA/MET IR FDC NDA (204-353). Does the Agency agree with this approach?

**FDA Response: We agree with this proposal. Financial disclosure information is required only for covered clinical studies not previously submitted.**

**Question 9:** As recommended by the Agency in its meeting minutes to the FDC EOP2 meeting held on 30 August 2010, the Sponsor intends to submit the CANA/MET IR FDC NDA (204-353) as a 505(b)(2) application. The Sponsor plans to rely on NDA 20-357 for GLUCOPHAGE to support the safety and efficacy of metformin. Does the Agency agree that cross-referencing the nonclinical and clinical information from NDA 20-357 for GLUCOPHAGE is sufficient and submitting published literature on metformin is not necessary for the CANA/MET IR FDC NDA (204-353) filing?

**FDA Response: We agree with this proposal. A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. 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 Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>.**

When submitting 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 the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which we consider to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify

the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

**Additional regulatory comments:**

- A. In your submission of a 505(b)(2) application, you should clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any of the published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, you should include a copy of the article(s) in your submission.**

**In addition to identifying the source of supporting information in your annotated labeling, your marketing application should summarize the information that supports the application in a table similar to the one below.**

<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA 012345 “DRUGNAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA 201223 “DRUGNAME”</i>	<i>Previous finding of safety for carcinogenicity</i>
<i>4.</i>	

- B. We remind you that your labeling must conform to the Physicians Labeling Rule (PLR) format and that 505(b)(2) marketing applications are subject to the Prescription Drug User Fee Act.**

**Question 10:** The Sponsor proposes referring to the published literature in the canagliflozin tablet NDA (204-042) (and corresponding 4MSU) and only submitting new published information relevant to the CANA/MET IR FDC NDA (204-353). Does the Agency agree with this proposal?

**FDA Response: We agree with this proposal.**

**Question 11:** The CANA/MET IR FDC NDA (204-353) will include the same Phase 3 studies as the canagliflozin tablet NDA (204-042) as agreed with the Agency at the FDC EOP2 meeting (30 August 2010). With the exception of a Phase 2 study and Phase 1 bioequivalence and food effect studies, the available efficacy data at the time of the CANA/MET IR FDC NDA (204-353) is the same as the available efficacy data in the canagliflozin tablet NDA (204-042). Accordingly, does the Agency agree that cross-referring to the ISE in the canagliflozin tablet NDA (204-042) and adding an addendum to provide for the canagliflozin/metformin IR FDC-specific Phase 2 study and Phase 1 studies fulfills the requirements for an ISE under 201 CFR 314.50(d)(5)(v) for the CANA/MET IR FDC NDA (204-353)? In addition, the sponsor proposes to provide a new Module 2.7.3 Summary of Clinical Efficacy in the CANA/MET IR FDC NDA (204-353).

**FDA Response: Refer to our response to Question 7 with regard to providing summaries and cross-referencing data from NDA 204042.**

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**Additional Clinical Pharmacology comment:**

**Clarify whether the to-be-marketed formulation of the CANA/MET IR FDC was used in the bioequivalence trials - DIA1038, DIA1046, DIA1050, and DIA1051.**

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MARY H PARKS  
08/30/2012

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 204353

**LATE-CYCLE MEETING MINUTES**

Janssen Pharmaceuticals Inc.  
c/o Janssen Research & Development, LLC  
Attention: Brandon D. 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 December 12, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for canagliflozin and metformin hydrochloride immediate release tablets 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 12, 2013.

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

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 (Acting)  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** September 12, 2013 12:00 to 1:00PM EDT  
**Meeting Location:** 10903 New Hampshire Avenue  
Building 22, Conference Room # 1415  
Silver Spring, MD 20903  
**Application Number:** NDA 204353  
**Product Name:** canagliflozin/ metformin hydrochloride immediate release tablets  
**Applicant Name:** Janssen Pharmaceuticals Inc.  
**Meeting Chair:** Jean-Marc Guettier, MD  
**Meeting Recorder:** Abolade (Bola) Adeolu

**FDA ATTENDEES**

Jean-Marc Guettier, MD- Director (Acting), Division of Metabolism & Endocrinology Products (DMEP)  
Hyon Kwon, PharmD- Clinical Reviewer, DMEP  
Todd Bourcier, PhD – Nonclinical Supervisor, DMEP  
Fred Alavi, PhD - Nonclinical Reviewer, DMEP  
Chandra Sahajwalla, PhD – Director, Division of Pharmacology 2 (DCPII), Office of Clinical Pharmacology (OCP)  
Lokesh Jain, PhD - Clinical Pharmacology Team Lead, DCPII, OCP  
Ritesh Jain, PhD – Clinical Pharmacology Reviewer, DCPII, OCP  
Vikram Sinha, MD – Director, Division of Pharmacometrics, OCP  
Nitin Mehrotra, PhD – Team Lead, Division of Pharmacometrics, OCP  
Mark Rothmann, PhD – Lead Mathematical Statistician, Division of Biometrics II (DBII)  
Wei Liu, PhD- Statistical Reviewer, DBII  
Okpo Eradiri, PhD- Biopharmaceutics Reviewer  
Ali Niak, MD- Medical Officer, Office of Surveillance & Epidemiology (OSE), Division of Pharmacovigilance I (DPVI)  
Christine Chamberlain, PharmD, BCPS, CDE- Safety Evaluator, OSE, DPVI  
Min Chu Chen, MS, RPh – Director (Acting), OSE, DPVI  
Amarilys Vega, MD, MPH – Medical Officer, OSE, Division of Risk Management  
Mehreen Hai, PhD –Safety Regulatory Project Manager  
Elizabeth Chen, PharmD - Regulatory Project Manager  
Julie Marchick, MPH - Chief, Project Management Staff  
Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

**EASTERN RESEARCH GROUP ATTENDEES**

Patrick J. Zhou, Independent Assessor

## **APPLICANT ATTENDEES**

### **Compound Development Team**

Kirk Ways, MD, PhD - Development Head Metabolism

Norman Rosenthal, MD - Vice President, Canagliflozin Compound Development Team Leader

Hamish Ross, PhD - Vice President, Clinical Research, Canagliflozin/Metformin FDC

Compound Development Team Leader

### **Clinical Pharmacology, Translational Medicine, Pharmacogenomics, and Pharmacometrics**

Kenneth Turner, PhD - Clinical Pharmacology Therapeutic Area Head

Damayanthi Devineni, PhD - Director, Clinical Pharmacology Leader

Willem De Winter, PhD - Scientific Director, Model Based Drug Development

David Polidori, PhD - Head of Clinical and Translational Biomarkers, Cardiovascular and Metabolism

### **Clinical**

Gary Meininger, MD - Franchise Medical Leader, Metabolism

### **Biostatistics & Programming**

Surya Mohanty, PhD - Clinical Biostatistics Head

Gordon Law, PhD - Director, Statistical Leader

### **Global Regulatory Affairs**

Jacqueline Coelln-Hough, RPh - Sr. Director, Global Regulatory Affairs

Brandon Porter, MBA - Associate Director, Regulatory Affairs

## **1.0 BACKGROUND**

NDA 204353 was submitted on December 12, 2012, for canagliflozin and metformin hydrochloride immediate release tablets 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

Proposed indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

PDUFA goal date: December 12, 2013

FDA issued a Background Package in preparation for this meeting on August 30, 2013.

## **2.0 DISCUSSION**

### **A. Substantive Review Issues**

We are repeating below our comments from the Late Cycle Meeting Background Package, issued on August 30, 2013, followed by the meeting discussion and post-meeting comments in *bold italic* font.

**Clinical Pharmacology**

1. Based on the available concentration range, the data submitted in NDA 204042 do not show a robust relationship between plasma canagliflozin concentrations and HbA1c response for canagliflozin. The PK/PD model developed based on the current data has several limitations and is inadequate to bridge the QD and BID dosing regimen.

a)  (b) (4)

b) 

c) 

***Discussion: See our post-meeting comments below, regarding the limitations of your current modeling approach. We encourage you to consider these comments while developing a modeling and simulation (M&S) plan to address the bridging between QD and BID dosing regimen. Please submit the details of your M&S plan for Agency review prior to initiation of your modeling effort.***

i.  (b) (4)

*ii.*

*iii.*

*iv.*

*v.*

*vi.*

**Clinical**

2. As discussed during the mid-cycle teleconference and written communication dated June 6, 2013, the magnitude of the HbA1c reduction observed at 18-weeks in Study DIA2003 (i.e., - 0.4% for 50 mg BID dose), when canagliflozin is administered twice daily, was numerically smaller than the HbA1c reduction observed at 26-weeks in Study DIA3006 (i.e., -0.6% for the 100 mg QD dose), when canagliflozin is administered once daily (Study DIA3006). You have attempted to bridge differences in observed efficacy across the two studies using posthoc analyses which were not pre-specified. Post-hoc comparisons of efficacy across clinical studies have several limitations and can be confounded by many known and unknown factors. In the absence of a well-established

plasma canagliflozin exposure HbA1c response relationship, the clinical data submitted in NDA 204353 is not adequate to bridge the efficacy.

***Discussion:*** *It was reiterated that single arm, cross-trial, post-hoc and/or subgroup analyses would not address the clinical pharmacology deficiency listed above.*

### **Statistics**

3. The bootstrap procedure you have proposed to bridge the QD and BID dosing regimens only accounts for a single known prognostic factor. It does not account for other known or unknown prognostic factors, or for environmental/study differences between the two studies. This is a common issue with any across trials comparison. The bootstrap procedure can therefore not be used as a substitute for a comparison within a randomized study.

***Discussion:*** *No discussion occurred*

## **B. Postmarketing Requirements/Postmarketing Commitments**

The following potential postmarketing requirements/commitments were conveyed in the Late Cycle Meeting Background Package. No significant meeting discussion occurred.

- a) A 26-week, randomized double-blind, placebo-controlled study, followed by a 26-week double-blind, placebo-or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus, as add-on to metformin.

- b)  (b) (4)

- c) A study to evaluate the swallowability of Invokamet tablet in pediatric patients.
- d) Additionally, if a new pediatric formulation of Invokamet is contemplated for marketing, you will be required to conduct the following:

A clinical pharmacology study in pediatric patients, ages 10 to 17 years (inclusive), with type 2 diabetes comparing the pharmacokinetics of Invokamet to co-administered canagliflozin and metformin hydrochloride immediate-release tablets. As part of this study, you may evaluate whether pediatric patients can safely swallow the Invokamet tablet.

NDA 204353  
Late-Cycle Meeting Minutes

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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JEAN-MARC P GUETTIER  
09/26/2013



NDA 204353

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

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

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invokamet (canagliflozin and metformin hydrochloride) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 12, 2013. Attached is our background package, including our agenda, for this meeting.

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 (Acting)  
Division of Metabolism & Endocrinology Products  
Office of Drug evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** September 12, 2013 12:00 to 1:00 PM

**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room Number: 1415  
Silver Spring, MD 20903

**Application Number:** NDA 204353

**Product Name:** Invokamet (canagliflozin and metformin hydrochloride) tablets

**Indication:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

**Sponsor/Applicant Name:** Janssen Pharmaceuticals, Inc.

## INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

## BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

### 1. Discipline Review Letters

No Discipline Review letters have been issued to date

## 2. Substantive Review Issues

### Clinical Pharmacology

1. Based on the available concentration range, the data submitted in NDA 204042 do not show a robust relationship between plasma canagliflozin concentrations and HbA1c response for canagliflozin. The PK/PD model developed based on the current data has several limitations and is inadequate to bridge the QD and BID dosing regimen.



### Clinical

2. As discussed during the mid-cycle teleconference and written communication dated June 6, 2013, the magnitude of the HbA1c reduction observed at 18-weeks in Study DIA2003 (i.e., -0.4% for 50 mg BID dose), when canagliflozin is administered twice daily, was numerically smaller than the HbA1c reduction observed at 26-weeks in Study DIA3006 (i.e., -0.6% for the 100 mg QD dose), when canagliflozin is administered once daily (Study DIA3006). You have attempted to bridge differences in observed efficacy across the two studies using post-hoc analyses which were not pre-specified. Post-hoc comparisons of efficacy across clinical studies have several limitations and can be confounded by many known and unknown factors. In the absence of a well-established plasma canagliflozin exposure HbA1c response relationship, the clinical data submitted in NDA 204353 is not adequate to bridge the efficacy

of twice daily canagliflozin to that of once daily canagliflozin.

### **Statistics**

3. The bootstrap procedure you have proposed to bridge the QD and BID dosing regimens only accounts for a single known prognostic factor. It does not account for other known or unknown prognostic factors, or for environmental/study differences between the two studies. This is a common issue with any across trials comparison. The bootstrap procedure can therefore not be used as a substitute for a comparison within a randomized study.

### **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

### **REMS OR OTHER RISK MANAGEMENT ACTIONS**

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology determined that a REMS is not necessary. We will make a final determination for the need for a REMS once the review of your application is complete.

### **LCM AGENDA**

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 45 minutes

Each issue will be introduced by FDA and followed by a discussion.

- a) Clinical Pharmacology
- b) Clinical
- c) Statistics

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- a) A 26-week, randomized double-blind, placebo-controlled study, followed by a 26-week double-blind, placebo-or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus, as add-on to metformin.

- b)



(b) (4)

(b) (4)

- c) A study to evaluate the swallowability of Invokamet tablet in pediatric patients.
- d) Additionally, if a new pediatric formulation of Invokamet is contemplated for marketing, you will be required to conduct the following:

A clinical pharmacology study in pediatric patients, ages 10 to 17 years (inclusive), with type 2 diabetes comparing the pharmacokinetics of Invokamet to co-administered canagliflozin and metformin hydrochloride immediate-release tablets. As part of this study, you may evaluate whether pediatric patients can safely swallow the Invokamet tablet.

4. Wrap-up and Action Items – 5 minutes

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/s/  
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JEAN-MARC P GUETTIER  
08/30/2013