

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204042Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA 204042

SUPPL: N/A

HFD-510

Trade Name Invokana

Generic Name canagliflozin tablets

Applicant Name Janssen Pharmaceuticals, Inc.

Approval Date: March 29, 2013

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**

If yes, what type? Specify 505(b)(1)

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**

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.

N/A

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:

N/A

d) Did the applicant request exclusivity? **YES**

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety? **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?

N/A

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? **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.

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.

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.) N/A

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

NDA#

NDA#

NDA#

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.

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?

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?

(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.

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?

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

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does

Investigation #2

IND

!
!
! 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

Explain:

!
!
! NO
! Explain:

Investigation #2

YES

Explain:

!
!
! NO
! 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.)

If yes, explain:

=====

Name of person completing form: Jena Weber
Title: RHPM

Date: 3/1/13

Name of Office/Division Director signing form: Mary Parks, M.D.
Title: Division Director, DMEP

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

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

/s/

JENA M WEBER
03/29/2013

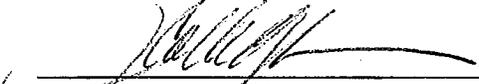
MARY H PARKS
04/01/2013

Janssen Research & Development, LLC.
Global Regulatory Affairs



DEBARMENT CERTIFICATION
Canagliflozin tablets NDA 204-042

Janssen Research & Development, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Jacqueline A. Coelln-Hough, R.Ph.
Senior Director, Global Regulatory Affairs
Cardiovascular / Metabolism Therapeutic Area

30 APRIL 2012
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA 204042		
Proprietary Name: canagliflozin tablets Established/Proper Name: Invokana Dosage Form: 100 & 300 mg tablets		Applicant: Janssen Pharmaceuticals
RPM: Jena Weber		Division: DMEP
<p><u>NDAs and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: 505(b)(1)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>N/A</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action: March 29, 2013 • User Fee Goal Date is March 31, 2013 	AP 3/29/13	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	None	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (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).

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	No
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? 	No
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	N/A
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	N/A
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	N/A
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	No
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	Verified
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	N/A

<ul style="list-style-type: none">• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?</p> <p>(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If “Yes,” skip to question (4) below. If “No,” continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.</i></p> <p><i>If “No,” continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p> <p><i>If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p> <p>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “No,” continue with question (5).</i></p>	<p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p> <p>N/A</p>
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<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p>N/A</p>
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CONTENTS OF ACTION PACKAGE

<p>❖ Copy of this Action Package Checklist⁴</p>	<p>Yes</p>
Officer/Employee List	
<p>❖ 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>)</p>	<p>Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p>Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>AP 3/29/13</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>3/29/13</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>5/31/2012</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<p>N/A</p>

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ 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>)	Final 3/29/13
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	3/29/13
<ul style="list-style-type: none"> Original applicant-proposed labeling 	3/13/13 (annotated)
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	3/21/13
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	AC Reviews:10/4/12, 1/30/13 (DMEPA) Letter: 10/4/12
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 3272713 <input checked="" type="checkbox"/> DMEPA 2/3/13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) <input checked="" type="checkbox"/> SEALD 3/28/13 Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	3/29/13
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	3/29/13
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	No
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>2/13/13</u> If PeRC review not necessary, explain: Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FD RR (do not include previous</i>	2/15/12, 6/4/12, 7/5/12, 8/2/12,

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<i>action letters in this tab), emails, faxes, telecons)</i>	8/17/12, 9/5/12, 11/15/12, 11/19, 11/27, 12/12 (2), 12/18 (2), 12/25, 12/31/12 (2), 1/11, 3/3 (2), 3/13, 3/15/3/25/13.
❖ Internal memoranda, telecons, etc.	No
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	No meeting
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	N/A
• Pre-NDA meeting (<i>indicate date of mtg</i>)	4/13/12
• EOP2 meeting (<i>indicate date of mtg</i>)	4/28/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	N/A
❖ Advisory Committee Meeting(s)	Yes
• Date(s) of Meeting(s)	1/10/13
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	Summary Min. 3/5/13
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	3/29/13
Division Director Summary Review (<i>indicate date for each review</i>)	3/25/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	3/25/13
PMR/PMC Development Templates (<i>indicate total number</i>)	3/28/13, total of 5
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	3/25/13
• Clinical review(s) (<i>indicate date for each review</i>)	2/11/13; 8/10/12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	See Clinical Review, page 21
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	DRUP – 12/4/12 DCRP – 12/2/12 OSE – 12/12/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	No REMS 2/5/13
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	2/12/13

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		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
Biostatistics		
❖ 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>		For safety: 2/4/13, 8/7/12 For efficacy: 2/12/13, 8/3/12
Clinical Pharmacology		
❖ 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>		2/12/13, 2/6/13, 8/22/12
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>		None
Nonclinical		
❖ 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>		2/7/13 3/27/13 (Tertiary P/T Review)
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		2/1/13 (Fred Alavi) 2/1/13 (Dan Minck) 7/31/12
❖ 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>		3/21/13
❖ ECAC/CAC report/memo of meeting		1/31/13
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>		None requested
Product Quality		
❖ 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>		2/13/13, 2/8/13, 8/2/12
❖ Microbiology Reviews		Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		Biopharm 2/11/13, 2/1/13, 8/10/12

❖ Environmental Assessment (check one) (original and supplemental applications)	
Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Yes, initial application EA CMC 2/4/13
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
NDA: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 3/28/13 Acceptable
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	Completed 2/4/13

⁷ 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.

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

/s/

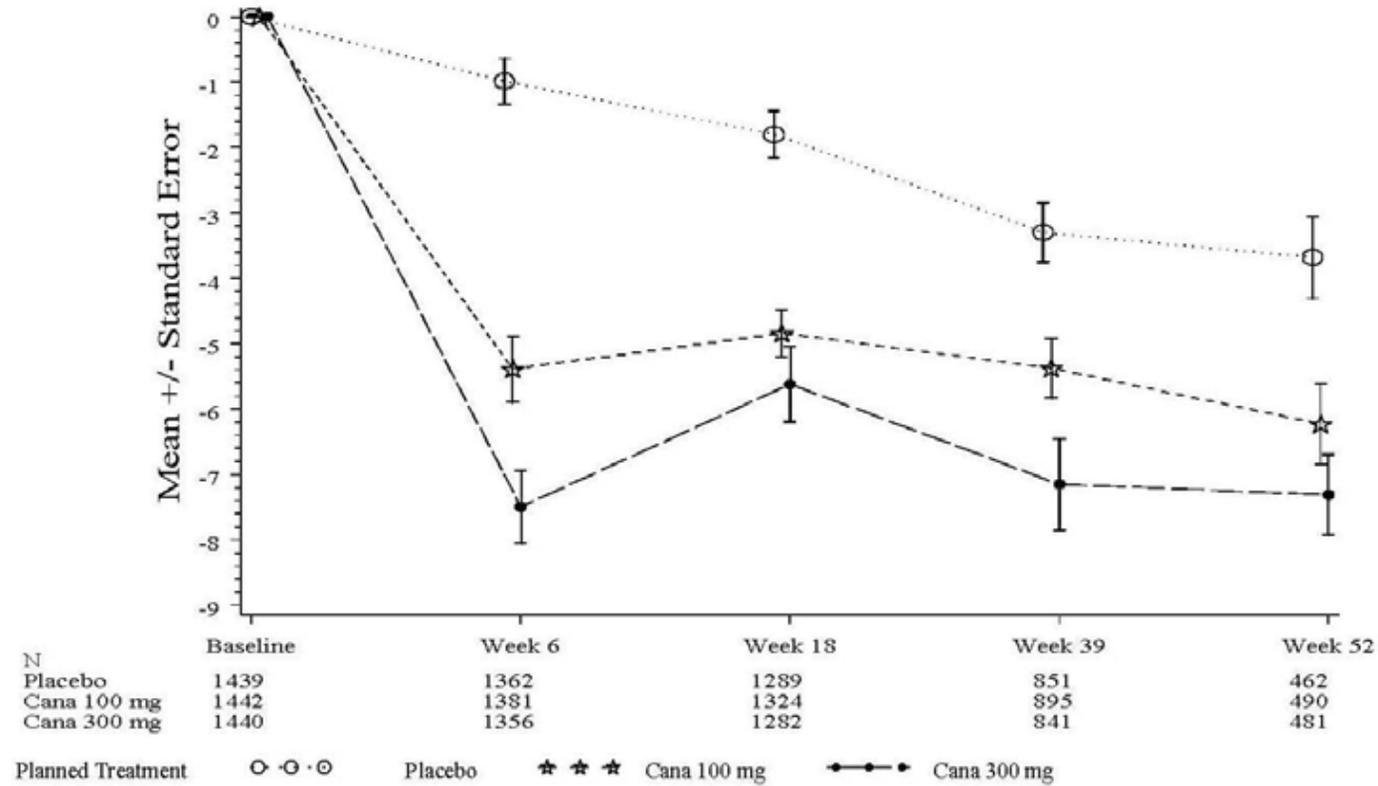
JENA M WEBER
03/29/2013

Sukhdev,

Please provide the following ASAP.

Request #1:

Similar to the following graph provided in your submission as Figure 20 in the ISS which describes the mean change in eGFR from baseline in DIA3008,



Please provide the same graph but by the patient subgroups with baseline of eGFR \geq 45-60 and eGFR \geq 30-45.

Request #2:

Please provide n(%) from your broad dataset and populate the following table.

	Control	Cana 100	Cana 300
<p>eGFR \geq 60</p> <ul style="list-style-type: none"> • any selected renal-related AEs • Any selected renal AEs leading to discontinuation • Any selected renal-related serious AEs • Reduction from baseline in eGFR > 30% <ul style="list-style-type: none"> ○ % concom use of loop diuretics ○ % concom use of ACE/ARBs ○ % use of diuretics and ACE/ARBs • Reduction from baseline in eGFR > 50% <ul style="list-style-type: none"> ○ % concom use of loop diuretics ○ % concom use of ACE/ARBs ○ % use of diuretics and ACE/ARBs 			
<p>eGFR \geq45-60</p> <ul style="list-style-type: none"> • any selected renal-related AEs • Any selected renal AEs leading to discontinuation • Any selected renal-related serious AEs • Reduction from baseline in eGFR > 30% <ul style="list-style-type: none"> ○ % concom use of loop diuretics ○ % concom use of ACE/ARBs ○ % use of diuretics and ACE/ARBs • Reduction from baseline in eGFR > 50% <ul style="list-style-type: none"> ○ % concom use of loop diuretics ○ % concom use of ACE/ARBs ○ % use of diuretics and ACE/ARBs 			

<p>eGFR \geq30-45</p> <ul style="list-style-type: none"> • any selected renal-related AEs • Any selected renal AEs leading to discontinuation • Any selected renal-related serious AEs • Reduction from baseline in eGFR > 30% <ul style="list-style-type: none"> ○ % concom use of loop diuretics ○ % concom use of ACE/ARBs ○ % use of diuretics and ACE/ARBs • Reduction from baseline in eGFR > 50% <ul style="list-style-type: none"> ○ % concom use of loop diuretics ○ % concom use of ACE/ARBs ○ % use of diuretics and ACE/ARBs 			

Thanks,
Jena

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/s/

JENA M WEBER
03/13/2013

We note a 9:1 imbalance in incident cases of prostate cancer not favoring canagliflozin at the 4 Months Safety Update cutoff. Most cases occurred > 120 days after randomization. You have provided narratives for 3 of these 9 cases.

Please update the number of prostate cancer cases that have been diagnosed up to now for each cana dose, all cana doses and all comparators. Provide updated sex-adjusted raw incidence (n/N for males) and incidence rate (n/PYE) for prostate cancer. Please provide narratives with all relevant clinical details for these cases. Please discuss how the observed incidence rate compares to expected incidence.

Please respond by COB Tuesday March 5, 2013.

Thanks,

Jena

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/s/

JENA M WEBER
03/03/2013

Request from clinical:

Serological or other clinical information to definitely rule out DILI is missing from several acute liver injury narratives. Update narratives for each of the following cases and include the current status of serological and PCR testing for each of these cases. In all narratives include the result for Hepatitis A,B,C,E, EBV, CMV and auto-immune hepatitises. Provide a reason for each case missing a full, standard, liver injury work up.

500611

601977

602724

602830

(b) (4)

(b) (4)

900392

903220

For each of these cases also please provide the opinion of each of the experts on the blinded adjudication committee.

Thanks,

Jena

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/s/

JENA M WEBER
03/03/2013

Executive CAC

Date of Meeting: January 29, 2013

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Tom Papoian, Ph.D., DCRP, Alternate Member
Todd Bourcier, Ph.D., DMEP, Team Leader
Fred Alavi, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Fred Alavi

NDA #204042

Drug Name: Canagliflozin (INVOKANA)

Sponsor: Janssen Pharmaceutical Inc.

Background:

Canagliflozin is a first in class inhibitor of renal tubule sodium-glucose co-transporter 2 (SGLT2) indicated for the treatment of type II diabetes. Canagliflozin is approximately 160 fold more selective to SGLT2 than SGLT1 but at high oral doses, canagliflozin has the potential to inhibit intestinal SGLT1. Canagliflozin lowers blood glucose by preventing renal tubular reabsorption of filtered glucose, resulting in glucosuria.

Mouse Carcinogenicity Study

Canagliflozin carcinogenicity was assessed at 10, 30 and 100 mg/kg/d 0.5% hypromellose in water in CD-1 mice. The survival rate across the dose groups was similar to control. No drug-related tumors were observed in mice. Systemic exposure at the 10, 30 and 100 mg/kg/d dose groups was 0.5x, 2x and 7x in males and 1x, 4x and 14x in females that in humans at the maximum recommended clinical dose of 300 mg QD, based on AUC.

Rat Carcinogenicity Study

Canagliflozin carcinogenicity was assessed at 10, 30 and 100 mg/kg/d 0.5% methocel in water in SD rats. The survival rates across the dose groups were similar to controls. Canagliflozin increased the incidence of renal tubular adenoma and carcinoma with statistical significance at 100 mg/kg/d in males and females. The incidence of adrenal pheochromocytoma was statistically significantly increased in males and numerically increased females at 100 mg/kg/d. The increased incidence in the females at 100 mg/kg was not significant in pairwise comparisons. Incidences of testicular Leydig cell tumors were increased with statistical significance at all doses in males. Mode of action studies conducted by the sponsor established reasonable evidence for carbohydrate malabsorption as a key event leading to both renal and adrenal tumors; however, a complete mode of action was not established. Canagliflozin doses of up to 600 mg per day did not cause carbohydrate malabsorption in clinical trials. The testicular Leydig cell tumors were associated with a 2-fold increase in luteinizing hormone (LH) in male rats, which

have been reported to be exceptionally sensitive to elevations in LH. There was no change in LH in clinical trials. The testicular tumors were therefore considered not clinically relevant. Systemic exposure at the 10, 30 and 100 mg/kg/d dose groups was 1x, 5x, and 12x in males and 2x, 7x, and 21x in females that at the maximum recommended clinical dose of 300 mg QD, based on AUC.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee agreed that the study was adequate, noting prior FDA concurrence with the protocol.
- The Committee concurred that the study did not produce drug related neoplasms.

Rat:

- The Committee agreed that the study was adequate, noting prior FDA concurrence with the protocol.
- The Committee concurred that renal tubular neoplasms at 100 mg/kg/d in males and females and adrenal pheochromocytomas at 100 mg/kg/d in males, as well as testicular Leydig cell tumors at all doses were clearly drug related. The Committee noted the numerical increase in pheochromocytomas in high dose females ($p = 0.07$).
- The Committee noted that the increase in serum LH in rats was considered the likely causative event for the Leydig cell tumors.
- The Committee noted that the sponsor provided reasonable evidence that malabsorption of dietary carbohydrate secondary to inhibition of intestinal SGLT1 was a likely key event in the development of the renal and adrenal neoplasms, but that a complete mode of carcinogenic action was not established.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\n
/Division File, DMEP
/Todd Bourcier DMEP
/Fred Alavi, DMEP
/Jena Weber, DMEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
01/31/2013

ABIGAIL C JACOBS
01/31/2013

Weber, Jena M

2

From: Berger, Mitchell (CBER)
dt: Monday, January 28, 2013 3:02 PM
to: Weber, Jena M; Kwon, Hyon
Cc: Suggs, Courtney; Greeley, George; Adeolu, Abolade; Marchick, Julie
Subject: RE: NDA 204042 (canagliflozin) - PeRC Date - Partial Waiver/Deferral/Plan-PeRC Feb. 13th

Follow Up Flag: Follow up
Due By: Monday, February 04, 2013 9:00 AM
Flag Status: Flagged

OK.... I have scheduled 204042 (canagliflozin) for Feb. 13th... Please have your materials (see Courtney's email below) completed by Monday, Feb. 4th... (b) (4)

Regards,

Mitchell

Mitchell Berger
Public Health Analyst/Project Manager-(Detail)
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave. Bldg 22, Room 6415
Silver Spring, MD 20993
Phone: (240) 402-5071
Email: Mitchell.Berger@fda.hhs.gov

From: Weber, Jena M
Sent: Monday, January 28, 2013 1:32 PM
To: Suggs, Courtney; Greeley, George
Cc: Marchick, Julie; Kwon, Hyon
Subject: RE: NDA 204042 (canagliflozin) - PeRC Date - Partial Waiver/Deferral/Plan
Importance: High

A NME, submitted May 31, 2012; UFGD is March 31, 2013, AC scheduled for January 10, 2013. Final reviews due in DARRTS 2/13/13.

We missed the Jan 23, 2013, meeting, so please reschedule ASAP. I will work with the MO to complete the required forms.

The company (Janssen, or JRD) is requesting a waiver for conducting pediatric studies in children 0 to <10 years of age and a deferral from providing pediatric in the ≥10 to <18 year-old population data as required by PREA, until a favorable risk/benefit in adults has been established.

Please let me know when you can place us on your calendar.

Thanks,
Jena

From: Suggs, Courtney
Date: Wednesday, October 03, 2012 12:43 PM
To: Weber, Jena M; Greeley, George
Cc: Marchick, Julie; Kwon, Hyon
Subject: RE: NDA 204042 (canagliflozin) - PeRC Date - Partial Waiver/Deferral/Plan

Hi Jena,

Canagliflozin is on the PeRC schedule for **January 23, 2013**. PeRC is usually held from 9 am to 12 am on Wednesdays. You will be notified of a specific time closer to the meeting date. Please send the completed documents covering ages birth to 16 years to be reviewed no later than **January 14, 2013**. Failure to do so will result in your product being rescheduled to a later date.

Please note that the templates in CDER Standard Letters (CSL) are not current so please be sure to use the forms on the PMHS website.

Here is the link to the PeRC information page where you will find the Pediatric Record and related templates:

<http://wcms.fda.gov/InsideFDA/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/UCM027829>.

The Pediatric Record (DARRTS) should reflect the opinions of the Division for each product and not merely those of the sponsor.

The Pediatric Plan submitted by the sponsor to support deferral requests MUST include a brief description of studies in addition to:

Protocol Submission Date
Study Completion Date
Final Report Submission Date

Thank you.

Courtney M. Suggs, Pharm.D., MPH

LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Weber, Jena M
Date: Tuesday, October 02, 2012 3:13 PM
To: Greeley, George; Suggs, Courtney
Cc: Marchick, Julie; Kwon, Hyon
Subject: NDA 204042 (canagliflozin)

A NME, submitted May 31, 2012; UFGD is March 31, 2013, AC scheduled for January 10, 2013.
Final reviews due in DARRTS 2/13/13.

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Please let me know when you can place us on your calendar.

Thanks,
Jena

Jena M. Weber
Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306

10903 New Hampshire Ave. Bldg 22, Room 6415
Silver Spring, MD 20993
Phone: (240) 402-5071
Email: Mitchell.Berger@fda.hhs.gov

From: Greeley, George
Sent: Monday, January 28, 2013 2:34 PM
To: Berger, Mitchell (CBER)
Cc: Suggs, Courtney
Subject: FW: NDA 204042 (canagliflozin) - PeRC Date - Partial Waiver/Deferral/Plan
Importance: High

Mitchell...don't know if Courtney sent this your way or not.

Thanks,
George

From: Weber, Jena M
Sent: Monday, January 28, 2013 1:32 PM
To: Suggs, Courtney; Greeley, George
Cc: Marchick, Julie; Kwon, Hyon
Subject: RE: NDA 204042 (canagliflozin) - PeRC Date - Partial Waiver/Deferral/Plan
Importance: High

A NME, submitted May 31, 2012; UFGD is March 31, 2013, AC scheduled for January 10, 2013. Final reviews due in DARRTS 2/13/13.

missed the Jan 23, 2013, meeting, so please reschedule ASAP. I will work with the MO to complete the required forms.

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Please let me know when you can place us on your calendar.

Thanks,
Jena

From: Suggs, Courtney
Sent: Wednesday, October 03, 2012 12:43 PM
To: Weber, Jena M; Greeley, George
Cc: Marchick, Julie; Kwon, Hyon
Subject: RE: NDA 204042 (canagliflozin) - PeRC Date - Partial Waiver/Deferral/Plan

Hi Jena,

Canagliflozin is on the PeRC schedule for **January 23, 2013**. PeRC is usually held from 9 am to 12 am on Wednesdays. You will be notified of a specific time closer to the meeting date. Please send the completed documents covering ages 0 to 16 years to be reviewed no later than **January 14, 2013**. Failure to do so will result in your product being rescheduled to a later date.

Please note that the templates in CDER Standard Letters (CSL) are not current so please be sure to use the forms on the PMHS website.



Here is the link to the PeRC information page where you will find the Pediatric Record and related templates:

<http://wcms.fda.gov/InsideFDA/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/UCM027829>.

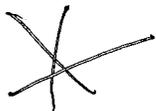
The Pediatric Record (DARRTS) should reflect the opinions of the Division for each product and not merely those of the sponsor.

The Pediatric Plan submitted by the sponsor to support deferral requests **MUST** include a brief description of studies in addition to:

Protocol Submission Date

Study Completion Date

Final Report Submission Date



Thank you.

Courtney M. Suggs, Pharm.D., MPH

LCDR, USPHS

Regulatory Project Manager

Pediatric and Maternal Health Staff

Office of New Drugs, Immediate Office

Center for Drug Evaluation and Research

US Food and Drug Administration

10903 New Hampshire Ave.

Building 22, Room 6471

Beltsville, MD 20993

Phone: (301) 796-2096

Email: courtney.suggs@fda.hhs.gov

From: Weber, Jena M

Sent: Tuesday, October 02, 2012 3:13 PM

To: Greeley, George; Suggs, Courtney

Cc: Marchick, Julie; Kwon, Hyon

Subject: NDA 204042 (canagliflozin)

A NME, submitted May 31, 2012; UFGD is March 31, 2013, AC scheduled for January 10, 2013. Final reviews due in DARRTS 2/13/13.

The company (Janssen, or JRD) is requesting a waiver for conducting pediatric studies in children 0 to <10 years of age and a deferral from providing pediatric in the ≥10 to <18 year-old population data as required by PREA, until a favorable risk/benefit in adults has been established.

Please let me know when you can place us on your calendar.

Thanks,
Jena

Jena M. Weber
Project Manager

See below; please address this in writing ASAP to your pending NDA file (NDA 204042).

This is in response to your submission dated 12/21/12 regarding the spec for the mutagenic impurity.

Thanks,
Jena

Your justification for setting the proposed (b) (4) limit to (b) (4) is predicated on a comparison of exposure to other endogenous/exogenous sources of (b) (4). This approach is useful to the extent that (b) (4) is similar to the other referenced substances.

The (b) (4) impurity and at least some of the referenced (b) (4) containing substances test positive in the Ames assay, with the mutagenic effect coming from the (b) (4) moiety of the structure. Beyond this observation, the degree of similarity between them becomes speculative.

Each of the (b) (4)-containing substances that you reference in support of a specification limit for your drug product differs substantially from (b) (4) in terms of molecular structure, and there is a lack of information to adequately assess similarity in terms of mutagenic potency, potential *in vivo* genotoxicity, and absorption, distribution, and metabolism of these mutagenic substances. Were (b) (4) reported prior to submission of the NDA, it is likely that additional *in vivo* genotoxicity studies would have been discussed to address this issue. Additionally, the intended use of and risk assessment for canagliflozin differs entirely from any of the (b) (4)-containing substances you cite.

Whether one invokes comparison to the dietary intake of (b) (4) (b) (4) we agree that the overall level of concern that consumers of canagliflozin will be exposed to unsafe levels of (b) (4) is low. However, choosing the dietary intake of (b) (4) as the primary basis for setting a limit is rather arbitrary, as comparison to many other (b) (4) substances was also discussed in your submission, each supporting a different limit. We consider your assessment supportive of overall safety but difficult to apply as a basis to set a specification for (b) (4). We recommend that the specification for the drug product be based on maximum levels of (b) (4) observed in the longest term stability batches to date, with an additional 2-fold increase to allow for unanticipated batch-to-batch variability. The maximum level reported from the 18-month stability tests is (b) (4) in the drug product, or (b) (4) for the 300mg tablet. Allowing a ~2-fold additional margin, we recommend the following specification:

Drug Product:

100mg: [REDACTED] (b) (4)

300mg: [REDACTED] (b) (4)

We note that the level of [REDACTED] (b) (4) in the drug product batches used in the pivotal clinical studies listed in Tables 3 and 4 of your 12 Nov 2012 submission fall below this recommended specification.

We ask that you provide a rationale if you believe that this proposed drug product specification for [REDACTED] (b) (4) represents an undue burden and must be increased to your originally proposed limit of [REDACTED] (b) (4)

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/s/

JENA M WEBER
01/11/2013

Please submit the following CMC information to your NDA file.

Thank you,
Jena

- 1) Provide engineering drawings, with appropriate dimensions, of all of your packaging components.
- 2) Provide specifications for cleanliness/contamination and defects as part of your acceptance criteria for all of your packaging components.
- 3) It is not clear from the container/closure section of your submission which of your (b) (4) bottles, corresponding to the NDC # 50458-140-50, in the How Supplied section of the Package Insert, is proposed for marketing 500 tablets of your (b) (4) strength drug product. In this connection, specify the count and the purpose of your (b) (4) bottles.

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/s/

JENA M WEBER
12/31/2012

Please provide the following information request since we could not reproduce your results on body weight based on the information submitted.

We are still not able to reproduce your results of body weight based on your ADVS datasets and the "Program Condition" (provided on December 19, 2012) for all the phase 3 studies (DIA3002, DIA3004, DIA3005, DIA3006, DIA3009, DIA3010, DIA3012, DIA3015, DIA3008 INS substudy and DIA3008 SU substudy) as well as the integrated data (moderate renal impairment).

For example, our SAS code and output for DIA3005 are below:

```

/*Study 3005 */
proc mixed data=advs(where=(window='WEEK 26 LOCF' and
param='Weight (kg)' and mitt='Y' and parcat1='PRIOR TO
RESCUE MEDICATION'));
by substudy;
class trtp ahastrat strata ;
model change= base trtp ahastrat strata ;
lsmeans trtp /cl pdiff=control('Placebo') alpha=0.05
adjust=dunnett;
run;

```

		Sub-study Identifier=Main				
Study Subject		-----				
		Least Squares Means				
Effect	Planned Treatment	Estimate	Standard Error	DF	t Value	
Pr > t	Alpha	Lower	Upper			
TRTP	Cana 100 mg	-2.4459	0.2116	570	-11.56	
<.0001	0.05	-2.8614	-2.0303			
TRTP	Cana 300 mg	-3.4224	0.2106	570	-16.25	
<.0001	0.05	-3.8359	-3.0088			
TRTP	Placebo	-0.5277	0.2130	570	-2.48	
0.0135	0.05	-0.9460	-0.1093			

Differences of Least Squares Means

DF	t	Planned Effect Value	Pr > t	Planned Treatment Adjustment	Estimate	Standard Error
570	-6.43	TRTP Cana 100 mg	<.0001	Placebo Dunnett-Hsu	-1.9182	0.2984
570	-9.73	TRTP Cana 300 mg	<.0001	Placebo Dunnett-Hsu	-2.8947	0.2975

Differences of Least Squares

Means

Adj Effect Lower	Planned Adj Treatment Upper	Planned Treatment Lower	Adj P Upper	Alpha	
2.5043	TRTP Cana 100 mg -1.3320	Placebo -2.5798	<.0001 -1.2565	0.05	-
3.4790	TRTP Cana 300 mg -2.3103	Placebo -3.5543	<.0001 -2.2351	0.05	-

-----Original Message-----

From: Weber, Jena M
 Sent: Thursday, December 20, 2012 7:52 AM
 To: Liu, Wei; Sahlroot, Jon T
 Cc: Kwon, Hyon; Guettier, Jean-Marc
 Subject: FW: Successfully Processed eCTD: nda204042 in
 DARRTS

NDA Amendment
 Response to Statistical Comments Received 18 December 2012

Thanks,
 Jena

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/s/

JENA M WEBER
12/31/2012

We are finding discrepancy in the mean and mean percent change from baseline, in particular with regard to the change from baseline for calcium regulatory axis analytes as shown in Table 39 of the Clinical Study Report for DIA3004. For example, in Table 39 of Clinical Study Report for DIA3004 describing changes from baseline in calcium regulatory axis analytes, the mean value at 26 week for serum 1,25-dihydroxy Vitamin D for placebo, cana 100, and cana 300 is shown as 67.28, 66.73, and 70.46 respectively. However, in Output DLAB51RM_CORE, the mean value at Week 26 for serum 1,25-dihydroxy Vitamin D is shown as 65.83, 65.42, and 70.25 for placebo, cana 100, and cana 300 respectively. This translates into difference mean change from baseline and mean % change from baseline than what is presented in Table 39 and Output DLAB51RCM_CORE. Please double check the calculation of mean change from baseline and mean % change from baseline for the data presented in Table 39, and submit the accurate data.

Please respond by December 28, 2012.

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/s/

JENA M WEBER
12/25/2012

- Provide data for the following table for each trial:

Table 1: Use of Statin Drugs Before and After Starting Study Drug by Treatment Arm in Each Phase 3 Trial

	Placebo	Cana 100	Cana 300	Glimepiride	Sitagliptin
DIA3002					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3005					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3006					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3012					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3004					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3008					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3009					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3010					
At baseline, n/N (%)					
After starting study drug, n/N (%)					
DIA3015					
At baseline, n/N (%)					
After starting study drug, n/N (%)					

- The reference tables for LDL-C subgroup data at the end of section 2.3.3.3.4 in the Summary of Clinical Safety only provide data for the mean **absolute** change in LDL from baseline for each subgroup factors; provide similar reference tables for the mean **percent** change in LDL from baseline for each subgroup factors (in conventional units).
- Provide baseline characteristics for subjects who had cardiovascular (CV) event in DIA3008 per group as specified in the table:

	Canagliflozin Subjects with CV event within 30 days (n=13)	Canagliflozin Subjects with CV event after 30 days (N=95)	Placebo All subjects with CV event (N=53)
Age:			
Mean [SD]			
≥65 years, n (%)			
Male, n (%)			
Caucasian, n (%)			
Mean [SD] HbA1c (%)			

Mean [SD] duration of diabetes (years)			
eGFR (mL/min/1.73m ²) Mean [SD] <60, n (%)			
Subjects with microvascular complications, n (%)			
Subjects with diabetic nephropathy, n (%)			
Subjects with diabetic retinopathy, n (%)			
Mean [SD] systolic blood pressure (mmHg)			
Mean [SD] diastolic blood pressure (mmHg)			
Mean [SD] LDL (mg/dL)			
Mean [SD] weight (kg)			
BMI Mean [SD] (kg/m ²) ≥30, n (%)			
Smoker, %			
Risk of CV events, n (%): Primary prevention Secondary prevention			
History of hypertension, n (%)			
History of MI, n (%)			
History of stroke, n (%)			
History of dyslipidemia, n (%)			
Concomitant drugs, n (%): Renin-angiotensin agent Statin Diuretics Loop diuretics Anti-thrombotic agents			
Subjects with number of cardiovascular risk factor, n (%): 1 2 3 >3			
Cardiovascular risk factor, n (%): Current smoker Diabetes history ≥10 years HDL-C (<39 mg/dL) Micro or macro-albuminuria SBP> 140 mmHg at screening			

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/s/

JENA M WEBER
12/18/2012
IR - Clinical

We are able to reproduce your results of the primary endpoint HbA1c for the LOCF population. However, we are not able to reproduce your results of the secondary efficacy endpoint, body weight based on your ADVS datasets and the "Program Condition" (provided on December 4, 2012) for all the phase 3 studies (DIA3002, DIA3004, DIA3005, DIA3006, DIA3009, DIA3010, DIA3012, DIA3015, DIA3008 INS substudy and DIA3008 SU substudy) as well as the integrated data (moderate renal impairment).

For example, in study DIA3008 sulphonylurea substudy (population 1) we obtained the following adjusted mean changes from baseline for body weight using LOCF (window='WEEK 18 LOCF', param='Weight (kg)', and parcat1='PRIOR TO RESCUE MEDICATION'):

<u>Placebo</u>	<u>Canagliflozin</u>	
	<u>100 mg</u>	<u>300 mg</u>
-0.17 (n=190)	-0.80 (n=191)	-1.05 (n=194)

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/s/

JENA M WEBER
12/18/2012

To clarify our request #3:

Please clarify why you are log transforming both baseline eGFR and proteinuria in your proposed models. Do you have evidence that data for both of these variables is severely skewed right?

We are interested in evaluating whether the treatment effect differs according to baseline eGFR. Your model should therefore include a treatment by baseline eGFR interaction term and you should test the significance of this interaction.

For example, the model we are interested in for baseline eGFR is:

HbA1c change = Treatment + TRIAL# stratification factor + baseline HbA1c + baseline eGFR + interaction of treatment X baseline eGFR.

We are also interested in evaluating whether the treatment effect differs according to baseline proteinuria. Your model should therefore include a treatment by baseline proteinuria interaction term, and you should test the significance of this interaction.

For example, the model we are interested in for proteinuria is:

HbA1c change = Treatment + TRIAL# stratification factor + baseline HbA1c + baseline albumin: creatinine ratio (ACR) + interaction of treatment X baseline albumin: creatinine ratio (ACR).

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/s/

JENA M WEBER
12/12/2012

Marchick, Julie

From: Marchick, Julie
Sent: Friday, December 07, 2012 10:42 AM
To: 'Saran, Sukhdev [JRDUS]'
Cc: Weber, Jena M
Subject: NDA 204042 Canagliflozin - Information Request

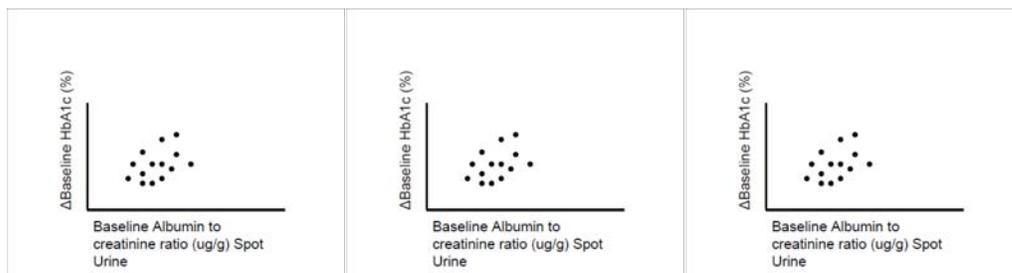
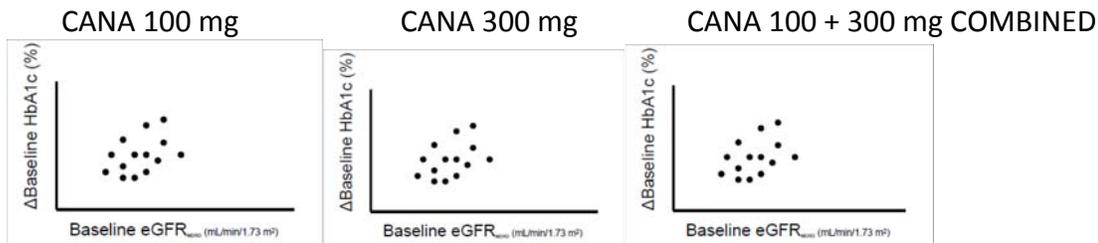
Attachments: Picture (Enhanced Metafile); Picture (Enhanced Metafile)

Sukhdev,

We have another information request for you. We ask that you submit your responses by December 14.

- 1) Plot baseline eGFR based on the 4-variable MDRD and the unadjusted change from baseline in HbA1c to end of treatment using the randomized population treated with at least one dose of investigational agent in the following datasets and individual studies: DS-1, DS-2, DIA-3004 and DS-3 for each dose, for the combination and for placebo/comparator (see examples below; note placebo not shown). HbA1c data can be censored at the time of rescue and LOCF can be used to impute missing data.
- 2) Plot the relationship between baseline proteinuria and the unadjusted change from baseline in HbA1c to end of treatment in the randomized population treated with at least one dose of investigational agent (modified intent to treat or mITT population with LOCF) for all trials where a baseline spot urine albumin to creatinine ratio was collected (e.g., DIA3004 and DIA3008). HbA1c data can be censored at the time of rescue and LOCF can be used to impute missing data. Repeat these analyses in the subgroup of individuals who underwent 24-hour urine collection for proteinuria in DIA-3004.
- 3) Perform linear regression analyses to evaluate the relationship between baseline eGFR and baseline proteinuria in the (modified intent to treat or mITT population with LOCF) and the change in HbA1c from baseline to end of treatment adjusting for factors used in your primary analysis model (i.e., baseline HbA1c, OAD and relevant stratification) excluding factors related to baseline eGFR and proteinuria from the models. Show separate plots for each cana dose groups, for a combined cana group and placebo/comparator group perform these analyses for: DS-1, DS-2, DIA-3004 and DS-3.

Examples:



Thanks,
Julie

Julie Marchick
Chief, Regulatory Project Management Staff

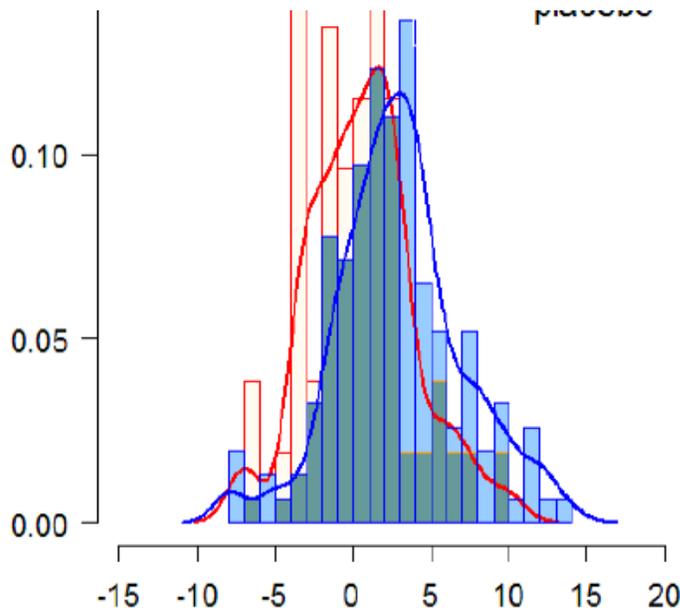
**Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov**

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/s/

JULIE C MARCHICK
12/07/2012

REQUEST 1: Provide figures using the example figure below depicting the frequency distribution of eGFR changes for each of the following comparisons; canagliflozin 100 mg versus placebo, canagliflozin 300 mg versus placebo, and canagliflozin pool versus placebo. In the first set of graphs (i.e., 3 comparisons), plot the peak change from baseline in eGFR on the x-axis in 0.5 mL/min/1.73 m² increments versus proportion of subjects. Repeat this analysis by plotting the change from baseline in eGFR at Week 6 for these same three comparisons. The graph formatting should allow adequate visualization of the distributions.



Provide these analyses for the following datasets: DS1, DS2, DIA3008, and two subgroups of DS2 by baseline eGFR (30 to <45 and 45 to <60).

Submit SAS programming condition for this analysis so that we can reproduce the results.

REQUEST 2: At 4-Month Safety Update, there were two additional renal cases meeting ESRD or renal transplantation criteria. Provide narratives for these two cases.

REQUEST 3: Provide data on the outcome of subjects who met PDLIC Criteria in DS2 similar to what is presented for DS3 in Table 96 of the Summary of Clinical Safety (SCS). In addition, provide trends in eGFR after discontinuation of study drug in DS2, similar to what is presented for DS3 in Figure 21 of the SCS.

REQUEST 4: Repeat the analysis used to generate Tables 95, 96, 106, and 107 of the SCS excluding active comparator data for DS3 (e.g., excluding subjects who were on glimepiride or sitagliptin, and only pooling placebo groups).

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/s/

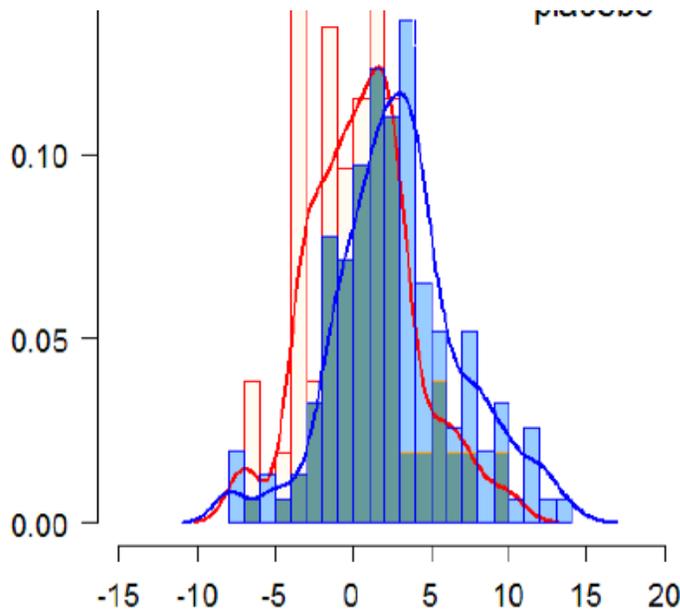
JENA M WEBER
12/05/2012

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/s/

JENA M WEBER
03/13/2013

REQUEST 1: Provide figures using the example figure below depicting the frequency distribution of eGFR changes for each of the following comparisons; canagliflozin 100 mg versus placebo, canagliflozin 300 mg versus placebo, and canagliflozin pool versus placebo. In the first set of graphs (i.e., 3 comparisons), plot the peak change from baseline in eGFR on the x-axis in 0.5 mL/min/1.73 m² increments versus proportion of subjects. Repeat this analysis by plotting the change from baseline in eGFR at Week 6 for these same three comparisons. The graph formatting should allow adequate visualization of the distributions.



Provide these analyses for the following datasets: DS1, DS2, DIA3008, and two subgroups of DS2 by baseline eGFR (30 to <45 and 45 to <60).

Submit SAS programming condition for this analysis so that we can reproduce the results.

REQUEST 2: At 4-Month Safety Update, there were two additional renal cases meeting ESRD or renal transplantation criteria. Provide narratives for these two cases.

REQUEST 3: Provide data on the outcome of subjects who met PDLIC Criteria in DS2 similar to what is presented for DS3 in Table 96 of the Summary of Clinical Safety (SCS). In addition, provide trends in eGFR after discontinuation of study drug in DS2, similar to what is presented for DS3 in Figure 21 of the SCS.

REQUEST 4: Repeat the analysis used to generate Tables 95, 96, 106, and 107 of the SCS excluding active comparator data for DS3 (e.g., excluding subjects who were on glimepiride or sitagliptin, and only pooling placebo groups).

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/s/

JENA M WEBER
12/05/2012

In continuing our review of your pending NDA (204042), please clarify the following regarding submitted datasets and LOCF population analyses.

We are not able to reproduce your primary analyses based on your model and submitted datasets on LOCF population for the following studies:

DIA3005 (both the Main and High glycemic sub-studies)

DIA3006

DIA3009

DIA3002

DIA3012

DIA3010

DIA3004

DIA3008 (Sulphonylurea and Insulin sub-studies) and the integrated dataset adlb0x for moderate renal impairment (HbA1c and body weight).

For example, in study DIA3005, we obtained the following adjusted mean changes from baseline for HbA1c using LOCF (window='WEEK 26 LOCF'):

<u>Placebo</u>	<u>Canagliflozin</u>	
	<u>100 mg</u>	<u>300 mg</u>
-0.17 (n=190)	-0.80 (n=191)	-1.05 (n=194)

We are able to reproduce your results for the Per Protocol populations.

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/s/

MARY H PARKS
11/27/2012

1. We are referring to the significant imbalance in CV events observed between Day 0-30 of DIA3008.
2. We are requesting analyses of deep venous thrombotic and pulmonary embolic events for this time period. You should present several analyses based on the capture strategy used in the NDA (i.e., SMQ capture strategy, eCRF capture strategy), the nature of the event (leading to death, leading to discontinuation, serious event, all events) and type of event adjudicated versus not adjudicated.

Thanks,
Jena

From: Saran, Sukhdev [JRDUS] [mailto:SSaran@its.jnj.com]
Sent: Friday, November 16, 2012 2:42 PM
To: Weber, Jena M
Subject: RE: see attached - Clarification to Clinical Comments/Requests

Hi Jena,

We have two clarification questions regarding the Divisions comments /requests. Could you please forward these to the reviewers?

FDA Request #7:

We note a significant imbalance in early cardiovascular (CV) events in your premarket cardiovascular safety analysis. Provide us with your interpretation of the findings. In your interpretation please comment on the relationship between the observed findings of early volume contraction and hemo-concentration seen when initiating canagliflozin and these findings.

Clarification Question:

Specifically with reference to the KM curve for MACE Plus events, can you clarify what imbalance in early CV is being referenced?

FDA Request #8:

Provide a comparative (canagliflozin versus placebo and canagliflozin versus active comparator) analysis for all thrombotic events occurring between Day 0-and 30 after canagliflozin initiation for your up-dated (original + 4 month safety) safety database. Present the findings in terms of proportion and exposure adjusted incidence rates. In your response, provide us with your plan used for the analysis, list of preferred terms used to define thrombotic events and analysis datasets.

Clarification Question:

By thrombotic events are you requesting a comparison specifically for deep vein thrombosis/pulmonary embolic events?

Thanks,
Sukhdev

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/s/

JENA M WEBER
11/19/2012

Reference NDA 204042 (canagliflozin). We have completed our mid-cycle review for the **clinical** section of your submission and have the following comments and requests. Please address these in writing to your NDA file within 10 days.

If you have any questions, please call Ms. Jena Weber, at 301-827-1306.

1. We note that several cases of renal, bladder, and breast cancers reported to the IND are still blinded. We request that you un-blind and submit full narratives for these cases. Sufficient information in the narratives should allow the Agency reviewer to perform a drug causality assessment.
2. In addition, we request that you submit narratives for the additional cases of bladder, breast, and renal cancer reported in the 4-Month Safety Update (4MSU), and any additional cases reported since the data cutoff date for the 4MSU. Please flag cases that are duplicate between the IND and NDA.
 - a. Update incidence for these malignancies with all cases received to date. Present the findings in terms of proportions by treatment arm and in terms of exposure adjusted incidence rate by treatment arm.
 - b. Arrange narratives by type of cancer and treatment arm in your submission.
3. We also note that several cases of adrenal adenomas reported to the IND are still blinded. We request that you un-blind these cases and any other adrenal related cancer/neoplasm cases. We ask that you submit narratives and updated proportion and incidence rates as described above.
4. In the 4-month safety update (4MSU), you reported that there were 2 additional cases of bladder cancer in the canagliflozin treatment group (3 total cases with canagliflozin treatment group) and referenced table LAE64MAL_04_01JUL12. However, we only note 1 additional case of bladder cancer in the canagliflozin 300 mg treatment group in that table. Clarify this discrepancy.
5. In addition, in the 4MSU, you updated cases of breast cancer and reported a total of 7 and 5 cases in the canagliflozin 300 mg and non-canagliflozin treatment groups respectively. You again reference table LAE64MAL_04_01JUL12 to show this data. In this table however, we note 8 and 4 cases of breast cancer for canagliflozin 300 mg and non-canagliflozin treatment group respectively. Clarify this discrepancy.
6. We note imbalances in thyroid, skin, and intestinal cancers not favoring canagliflozin treated individuals. Submit incidence table by treatment arm (presenting proportions and exposure adjusted incidence rate) and narratives for all thyroid, skin, and intestinal cancers. Arrange narratives by type of cancer, reported Preferred Term (PT), and treatment arm.

- a. PTs for thyroid cancer should include thyroid adenoma, thyroid cancer, thyroid neoplasm, and any other thyroid cancer-related terms. PTs for skin cancers should include malignant melanoma, metastatic malignant melanoma, neuroendocrine carcinoma of skin, skin cancer, basal cell carcinoma, and any other skin cancer-related terms.

PTs for intestinal cancer should include colon adenoma, colon cancer, colon cancer metastatic, colorectal cancer, gastric adenoma, gastric cancer, gastrointestinal neoplasms, gastrointestinal tract adenoma, intestinal adenocarcinoma, rectal cancer, esophageal adenocarcinoma, esophageal carcinoma, and any other intestinal cancer-related terms.

Provide analysis and discuss differences between treatment arms for these malignancies, including assessment of risk factors and drug causality.

- 7. We note a significant imbalance in early cardiovascular (CV) events in your pre-market cardiovascular safety analysis. Provide us with your interpretation of the findings. In your interpretation please comment on the relationship between the observed findings of early volume contraction and hemo-concentration seen when initiating canagliflozin and these findings.

We are requesting information for the following subjects from study DIA3008 who had a CV event:

Subject ID
(b) (4)

(b) (4)



Provide the following information for these subjects in a tabular format:

- Subject ID
- Treatment arm
- Age
- Time of event (days since start of treatment)
- CV Event - for stroke, specify ischemic or hemorrhagic
- Outcome of CV Event
- Subject disposition after CV event - specify whether subject continued the therapy, and/or discontinued from study, etc
- Concomitant past medical history
- Concomitant medications and dose for each
- Baseline value & value at the time of CV event for: systolic and diastolic blood pressure, pulse rate, LDL cholesterol, blood urea nitrogen, serum creatinine, eGFR, hematocrit, hemoglobin, coagulation parameters, urinalysis and urine albumin to creatinine ratio if available.

In addition, provide case narratives for all these subjects.

8. Provide a comparative (canagliflozin versus placebo and canagliflozin versus active comparator) analysis for all thrombotic events occurring between Day 0-and 30 after canagliflozin initiation for your up-dated (original + 4 month safety) safety database. Present the findings in terms of proportion and exposure adjusted incidence rates. In your response, provide us with your plan used for the analysis, list of preferred terms used to define thrombotic events and analysis datasets.

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/s/

MARY H PARKS
11/15/2012



NDA 204042

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Janssen Pharmaceuticals, Inc
c/o: Janssen Research & Development, L.L.C
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Attention: Sukhdev K. Saran
Director, Global Regulatory Affairs

Dear Ms. Saran:

Please refer to your New Drug Application (NDA) dated May 31, 2012, received May 31, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Canagliflozin Tablets, 100 mg and 300 mg.

We also refer to your July 27, 2012, correspondence, received July 27, 2012, requesting review of your proposed proprietary name, Invokana. We have completed our review of the proposed proprietary name, Invokana and have concluded that it is acceptable.

The proposed proprietary name, Invokana, 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. Additionally, if **any** of the proposed product characteristics as stated in your April 23, 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 Jena Weber at (301) 796-1306.

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/

CAROL A HOLQUIST
10/10/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

October 5, 2012

10/5/12

Sukhdev K. Saran
Director, Global Regulatory Affairs, CV/IM
Janssen Research & Development
920 Route 202 South P.O. Box 300
Raritan, NJ, 08869-0602

Dear Ms. Saran:

We are in the process of developing the Agenda for the upcoming meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, which is tentatively scheduled for January 10, 2013. The committee will discuss the new drug application (NDA) 204042 canagliflozin, submitted by Janssen Research and Development LLC. Canagliflozin is a member of the sodium-glucose co-transporter 2 (SGLT2) inhibitors, and was developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Please note that the Federal Register (FR) Notice for this meeting has not yet been made publicly available and information pertaining to this meeting is not publicly releasable until that time. FR Notices are made available for public inspection one business day prior to official printing in the Federal Register. This is also referred to as an “advanced display” or “public inspection” document. The “advanced display” will be the first publically available access to the details of the meeting. You may check for advanced display publication through the following web site: <http://www.archives.gov/federal-register/public-inspection/index.html>; click on “View Tomorrow’s Federal Register”. You may also check to see if the FR notice is published by checking the web site: <http://www.gpo.gov/fdsys/browse/collection.action?collectionCode=FR>; click on the year, month, and date of publication, then click on “Food and Drug Administration”. If there were no FDA FR Notices published on a specific date, then the “Food and Drug Administration” link will not be viewable,

A timeline of significant due dates in the preparation for the advisory committee (AC) meeting is attached.

Prior to the Meeting:

- 1) **List of Investigators:** Please forward to me a searchable electronic copy of the list of investigators for all trials supporting the application(s) under review by October 23, 2012.
- 2) **Preparation and Submission of Briefing Materials for the AC Meeting:**

We are currently following the deadlines and instructions listed in the August 2008 Guidance for Industry “Advisory Committee Meetings — Preparation and Public Availability of Information

Given to Advisory Committee Members”. The link to the document may be found on the following URL address:

<http://www.fda.gov/oc/advisory/GuidancePolicyRegs/AC48HourFINALGuidance080408.pdf>

Most of the AC members will be receiving the electronic copies of the briefing materials on CD-ROMs. Please provide 35 electronic copies in Microsoft Word/Adobe PDF Version 8 or higher on separate CD-ROMs (in separate cases to protect them during mailing) and 12 of paper copies of your briefing materials. These copies must be received by me no later than close of business standard eastern time on December 7, 2012 (22 business days prior to the meeting). The package delivery address for FedEx and UPS is:

Paul Tran, R.Ph
Division of Advisory Committee and Consultant Management
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
WO31-2417
Silver Spring, MD 20993-0002
Phone: 301-796-9001

Please inform me immediately if you will be using a carrier other than those listed above, as I will need to make special arrangements for package pick-up. Be sure that the copies, both paper and electronic, are marked “ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE” as described in the Guidance, and that all CONFIDENTIAL markings in the headers, footers or watermarks of the pages, or the labels of the CD-ROMs, have been completely removed. Also, please send the memorandum, addressed to me, with your box of materials, in paper form separate from the briefing materials. Please be sure not to include official FDA forms (such as FDA form 356, *Application to Market a New Drug, Biologic, or an Antibiotic for Human Use*) as part of your briefing materials. I will then forward the copies to the Committee, the Division of Information Disclosure Policy, and to the reviewing division(s).

3) Meeting Participants

As soon as possible, please provide a preliminary list of all of the presenters and responders who will be representing you at the meeting, along with their affiliation(s). Representational activities include presenting, responding to questions, and/or sitting in the sponsor section at the meeting. Please send your final version of this list to me no later than December 19, 2012 (3 business weeks prior to meeting).

Please note that any current or former AC members, or other past or present Special Government Employees (SGE), who will be attending the meeting with you will be asked to complete the procedures in MaPP 6001.1 “Special Government Employees Representing Sponsors Before CDER”

(<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079920.pdf>), and should start this process as soon as possible. The goal is to avoid

situations in which a former member and/or consultant might inadvertently violate the law concerning representational activities.

It is a violation of ethics statutes 18 U.S.C. 203 and 205 for a Federal Employee, including (but not limited to) employees of the NIH, CDC, DoD, and VA, to represent a third party before another agency. Please note that Federal Employees will not be permitted to represent your company at the meeting.

The Committee Chair will be asking that each of your speakers (both presenters and responders), not employed by your company, to advise the Committee of any financial relationships that they may have with your company, such as consulting fees, travel expenses, honoraria, and other interests, including equity interests and those based upon the outcome of the meeting.

4) Final Agenda

I will also need to know the names and affiliations of your planned speakers and the titles of their presentations as soon as this information is available. Information received by December 26, 2012 (2 business weeks prior to meeting) will be included in the Final Agenda for the meeting.

Meeting Day Materials:

Please bring with you to the meeting at least 45 paper copies of any slides that will be presented at the meeting for use by the Committee members. At the end of the meeting day, we ask that you provide an electronic version of your slide presentations in Adobe PDF Version 8 or higher. If back-up slides are presented, we ask that you provide the backup slides in the same file as your core presentation. The slides will be also posted on the FDA web site after the meeting. The Guidance also encourages sponsors to bring a “reasonable number” of hard copies of the presentation slides for distribution to the public.

Additional Information Regarding AC Meeting Location:

The meeting of the Endocrinologic and Metabolic Drugs Advisory Committee will be held at the FDA White Oak Campus, in Building 31, the “Great Room” (Rm. 1503), White Oak Conference Center, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

Meeting Logistics:

Tour of the FDA Great Room

Please let me know as soon as possible if you and/or your audio/visual (A/V) company would like to tour the FDA Great Room. The Great Room is booked for other meetings well in advance. In order to schedule a tour during a time in which the Great Room available, we will need to know as soon as possible whether you wish to schedule a tour. It may be possible to test equipment during this tour if you wish.

Audio/Visual:

We will be working closely with you and any A/V company that you contract with to coordinate the A/V set up for this meeting and loading your equipment through the FDA loading dock prior to the meeting. Any A/V equipment that is larger than the screening machine in Building 1 will need to be brought in through the loading dock at Building 51. All large equipment will need to come in through the loading dock the day prior to the AC meeting by 2:30 p.m. This equipment can be stored in a locked room adjacent to the Great Room. Please note that FDA staff are frequently moving other equipment in and out of this locked room and are not responsible for your equipment. No large equipment can be brought in during the early morning hours on the day of the AC meeting as the loading dock is not open. Sponsors and their A/V company may arrive at the Great Room at 6:15 a.m. on the day of the meeting and can begin setting up equipment at this time. FDA's AV contact for this meeting is Thiep Vo. He can be reached at thiep.vo@fda.hhs.gov or by phone: (301) 796-9001.

Food Service on the Day of the AC Meeting:

Food service for the FDA White Oak Campus is through Sodexo. If you would like to use Sodexo, I can provide you with their contact information. There will also be a snack stand open during the meeting for the public. Sponsors may purchase food/beverage from this stand also. The snack stand will have limited sandwich and beverage options. If you wish to bring in outside food on the day of the meeting, you will need to bring this through Building 1 security. The food will need to fit through the screening machines in Building 1.

Room for Sponsor Use During the AC Meeting:

There are two rooms for Sponsor's use, which are located adjacent to the Great Room. You may be able to view these rooms on your scheduled tour. You will have access to these rooms from 6:15 a.m. on the day of the meeting until the conclusion of the day's meeting. These rooms will not have wired internet access and the wireless connection may be unreliable. These rooms will be your rooms for the entire day. We ask that you please vacate these rooms within one hour following the conclusion of the meeting.

Arriving at the White Oak Great Room on the Day of the AC Meeting:

All persons need to arrive through Building 1 to go through security and then walk directly to the Great Room. If you have been to the FDA White Oak Campus, Building 1 is the building at the head of the circle drive way. You are not required to provide FDA with the names of those entering through Building 1 on the AC meeting day for security purposes. Also, you are not required to complete the foreign visitor request form, in the event that you have a foreign national on your team. Lastly, you will not be required to have an escort or visitor badges on the day of the AC meeting.

AC Meeting Day Parking:

Your company can park its vehicles in the Southeast Surface lot on the FDA campus. The location of this lot can be found under "Driving Directions and Parking" on the following website:

<http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm> Any large vehicles can also be parked in this lot. Your vehicles can pick up your employees outside of Building 1 in the parking circle once the meeting has adjourned.

However, we ask that the vehicles do not park there until your employees are ready to leave the building as the parking circle can become very busy with taxis and other transportation services once a meeting has concluded.

Security:

If your company is planning to bring a security team with you on campus on the day of the AC meeting, please let me know as soon as possible as we will need to alert FDA security personnel of your security team's presence. FDA security may wish to speak to your security personnel prior to the AC meeting day.

Meeting Room Layout:

The meeting room layout is typical (a "U" shaped table for the committee members), with seats for the sponsor on one side and for the FDA on the other side. Limited seating may also be available in the audience for the sponsor.

I am the Designated Federal Officer for the committee and look forward to working with you. Please contact me at (301) 796-9029 or at paul.tran@fda.hhs.gov if you have any questions or concerns.

Thank you,

Paul Tran, R.Ph
Designated Federal Officer, EMDAC

There are 12 additional subjects with a MACE Plus event in datasets adcv and adttecvm (213 events) that do not appear in dataset adttecv (201 events). Why are these events missing in adttecv? Are they not included on table 195 of the ISS (page 435)? And should these events be included in the meta-analysis of CV events?

The 12 subjects are:

28431754DIA3004-049002-400373
28431754DIA3006 (b) (4)
28431754DIA3008
28431754DIA3008
28431754DIA3008
28431754DIA3008
28431754DIA3008
28431754DIA3008
28431754DIA3008
28431754DIA3008
28431754DIA3008
28431754DIA3009-011016-900217

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/s/

JENA M WEBER
09/05/2012



NDA 204042

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, L.L.C
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869

Attention: Sukhdev K. Saran
Director, Global Regulatory Affairs

Dear Ms. Saran:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Canagliflozin Tablets, 100 mg and 300 mg.

We acknowledge receipt of your July 27, 2012, correspondence, on July 27, 2012, notifying us that you are withdrawing your request for reconsideration of the proposed proprietary name, Invocana. This request for reconsideration of the proposed proprietary name is considered withdrawn as of July 27, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, 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 Jena Weber at (301) 796-1306.

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

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/s/

CAROL A HOLQUIST
08/02/2012



NDA 204042

FILING COMMUNICATION

Janssen Research & Development LLC
Attention: Sukhdev Saran
Associate Director, Regulatory Affairs
920 U.S. Highway; P.O. Box 300
Raritan, NJ 08869

Dear Ms. Saran:

Please refer to your New Drug Application (NDA) dated May 31, 2012, received May 31, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for canagliflozin Tablets, 100 mg and 300mg.

We also refer to your amendments dated June 29, July 5, and 27 (2), and August 10, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **March 31, 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, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 17, 2013.

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

1. Provide unique subject identifier by the Hepatic Event Assessment Committee (HEAC) Adjudication Criteria and treatment group as shown in the Table provided below for 56 subjects who were adjudicated for hepatic events. For 'Other' criteria, provide the liver injury-related preferred terms that led to adjudication for each subject.

Table: List of Subject Identifier by HEAC Adjudication Criteria and Treatment Group

HEAC Adjudication Criteria	Control	Cana 100 mg	Cana 300 mg
ALT \geq 5x ULN			
AST \geq 5x ULN			
ALT or AST \geq 5x ULN or TB \geq 2x ULN			
Other			

2. Clarify why there were 56 subjects who had liver events meeting adjudication criteria, and only 48 subjects are summarized in Tables 136 and 138 in the Summary of Clinical Safety.
3. Submit the GastrolPlus Model files.

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). 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 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.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, 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

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/s/

MARY H PARKS
08/17/2012

Jena,

I am fine with their plan.

Thanks,
Jaya

From: Weber, Jena M
Sent: Thursday, June 28, 2012 3:00 PM
To: 204042
Subject: FW: NDA 204-042 (Canagliflozin) - Minor Modifications

FYI, see below from Janssen. Let me know if you have any comments.

Thanks,
Jena

From: Saran, Sukhdev [JRDUS] [mailto:SSaran@its.jnj.com]
Sent: Thursday, June 28, 2012 2:55 PM
To: Weber, Jena M
Subject: NDA 204-042 (Canagliflozin) - Minor Modifications

Hi Jena,

Regarding our NDA 204-042 Submission dated 31 May 2012, we have noted a couple of items that require some minor modifications. These are noted below along with correction options that we would appreciate the Agency's feedback on.

- 1) Module 5.3.3.4 Extrinsic Factor PK Study Reports - Phase 1 Study 28431754-DIA-1034

Title: An Open-label, Two-period, Fixed-sequence Study to Explore the Effects of Multiple Doses of Hydrochlorothiazide on the Pharmacodynamics, Pharmacokinetics, and Safety of Multiple Doses of Canagliflozin in Healthy Subjects

Issue: The above granulated CSR is missing Appendix 13 – Discontinued Patients. This appendix appears in the report body list of appendices but there is no active link.

Correction Option: JRD proposes to submit an amendment to the NDA containing only Appendix 13 – Discontinued Patients for this study report (DIA1034). **Does the Agency agree?**

2) Module 5.3.1.2 - Comparative BA/BE Study Reports - Study from MTPC- TA-7284-03

Title: A clinical pharmacology study of TA-7284 in healthy adult male volunteers (Bioavailability study)

Issue: During translation to English, a single Japanese character was inadvertently retained on one page. In order to view it correctly, the Adobe Japanese Language Support Package is needed.

We have confirmed with the FDA e-submissions group that the FDA reviewers do not have this required Adobe Package, the error currently exists in the NDA submission that is on the FDA servers, and therefore, FDA reviewers will get an error message in trying to view this page. When the reviewers hit the "cancel" button, the affected page will become blank.

Correction Option: JRD proposes to submit an amendment to the NDA with a full corrected study report to delete the Japanese character; this will replace the report currently in the NDA. There are no other changes to the report. **Does the Agency agree?**

Please let me know if you would like to discuss these or if you have any questions.

Kind Regards,
Sukhdev

Sukhdev K. Saran, MBA, RAC

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/s/

JENA M WEBER
07/05/2012

MEMORANDUM OF TELECON

DATE: July 26, 2012

APPLICATION NUMBER: NDA 204042 canagliflozin

BETWEEN:

Name: Janssen Pharmaceuticals
Dorothy Linvill-Neal - Head, Global Trademark
Development, Janssen Global Services LLC
Valerie Donnelly - Director, Global Trademark
Development, Janssen Global Services LLC
Colleen Tavani - Trademark Development Project
Management Contractor, Janssen Global Services LLC
Paul Duwan - Global Marketing Leader, Janssen Global
Services LLC
John Otero - Director Marketing, Janssen Pharmaceuticals
Sukhdev Saran - Director, Regulatory Affairs, Janssen
Research & Development
Brandon Porter - Associate Director, Regulatory Affairs,
Janssen Research & Development

Phone: 1-888-624-7005

AND

Name: Division of Medication Error Prevention and Analysis
Kellie Taylor, PharmD - Deputy Division Director
Yelena Maslov, PharmD - TL
Reasol Agustin, PharmD - SE
Margarita Tossa, M.S. - SRPM

SUBJECT: Notification of decision regarding the reconsideration on proposed
proprietary name.

The Applicant was informed that DMEPA wanted to discuss preliminary findings and regulatory pathways forward relating to the proposed proprietary name Invocana.

Dr. Agustin told the company that DMEPA has completed review of the information submitted in support of the proposed proprietary name, Invocana and has concluded that the data provided by Janssen does not support the use of the proposed name for this product. Therefore, OSE/DMEPA continues to object to the use of the proposed proprietary name, Invocana due to possible confusion with the names [REDACTED] (b) (4) [REDACTED].

However, DMEPA took a preliminary look at the name Invokana (with a 'k') to see whether the change in letters from 'c' to 'k' would alleviate our safety concerns in relation to the names (b) (4). DMEPA's evaluation demonstrated that indeed due to the letter 'k', we are no longer concerned about confusion between Invokana and (b) (4) due to orthographic similarities. Thus, at this point the name Invokana (with a 'k') appears to look better than Invocana (with a 'c').

The applicant was advised to keep in mind that although DMEPA is no longer concerned with the confusion for the names (b) (4), we have not performed full promotional or safety evaluation of that name.

As a result, of DMEPA's evaluations of these names, DMEPA wanted the company to be aware of the two regulatory options:

1. Withdraw the proposed proprietary name Invocana and formally submit an alternate name, Invokana (with a k) for DMEPA's evaluation. Dr. Agustin and Dr. Maslov emphasized that this is not a guarantee of approval of the name. The same evaluation protocol still needs to be performed in order to fully assess the name from a medication error standpoint.

OR

2. Wait until DMEPA completes a full review and issues a formal denial letter on or close to August 29, 2012. Dr. Agustin noted that in this case, Janssen will be losing approximately a month of NDA clock, before they can submit the proposed name Invokana (with a 'k') for review to DMEPA, because the Division reviews one name at a time, and until a formal letter is issued or the name is officially withdrawn, and the secondary proprietary name is officially submitted, we will not be evaluating it.

The applicant agreed to withdraw the proposed name Invocana (with a 'c'). Once the name will be withdrawn, Janssen will submit a request for review of the proposed proprietary name Invokana (with a 'k') as a primary name, and also will include a secondary name as a back up. The applicant was also informed that the evaluation of the proposed proprietary name Invokana (with 'k') will be preformed according to PDUFA within 90 days from the date of the submission.

Margarita Tossa, M.S.
Safety Regulatory Project Manager
FDA/CDER/OSE/RMS

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/s/

MARGARITA V TOSSA
07/30/2012

YELENA L MASLOV
07/30/2012



IND 076479

MEETING MINUTES

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

Dear Ms. Saran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for canagliflozin (IND 076479).

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on Friday April 13, 2012. The purpose of the meeting was to discuss the content and format of the NDA.

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, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena M. Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

Meeting Minutes
Type B, pre-NDA

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Friday April 13, 2012, 11 a.m. – 12:30 p.m.
Meeting Location: White Oak Campus, Bld. 22, Conference Room 1415
Application Number: IND 076479
Product Name: Canagliflozin
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Janssen Research & Development, LLC
Meeting Chair: Mary Parks, M.D.
Meeting Recorder: Jena Weber, PM

FDA ATTENDEES

Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Somya Dunn, M.D.	Clinical Reviewer
Jean-Marc Guettier, M.D.	Acting Clinical Team Leader
Todd Sahlroot, Ph.D.	Biometrics Team Leader
Wei Liu, Ph.D.	Biometrics Reviewer
Janice Derr, MS	Biometrics Reviewer
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Acting Team Leader
Johnny Lau, Ph.D.	Clinical Pharmacology Team Leader
Susan Leibenhaut, M.D.	Office of Scientific Investigations
Amy Egan, M.D.	Deputy Director for Safety (DMEP)
Mehreen Hai, Ph.D.	Safety Project Manager
Cynthia LaCivita, RPh	Office of Surveillance and Epidemiology (OSE)
Quocbao Pham, RPh	OSE
Jena Weber, BS	Regulatory Health Project Manager

SPONSOR ATTENDEES

Mark Johnson, Ph.D.	Director, Pre-Clinical
Chris McShane	Manager, QM&C
Damayanthi Devineni, Ph.D.	Director, Clinical Pharmacology
Kirk Ways, M.D., Ph.D.	Compound Development Team Leader (Clinical)
Peter Stein, M.D.	Head of Development, Metabolism
Gary Meininger, M.D.	Franchise Medical Leader, Metabolism
Mehul Desai, M.D.	Sr. Director, Clinical Leader
Gordon Law, Ph.D.	Director, Statistical Leader

Meeting Minutes
Type B, pre-NDA

Surya Mohanty, Ph.D.	Clinical Biostatistics Head
Jacqueline Coelln-Hough, RPh	Sr. Director, Global Regulatory Affairs
Sukhdev Saram, MBA	Associate Director, Regulatory Affairs
Martin Kudlesky	Manager, Regulatory Affairs
Jeffy John	Sr. Associate, Regulatory Affairs
Lindsay Cobbs, RPh	Associate Director, Regulatory Affairs

BACKGROUND

The NDA will be submitted late May 2012, for canagliflozin tablet, and will include data from domestic and foreign clinical centers. Data from these locations will be pooled. The application will include data from 9 pivotal Phase 3 studies to establish safety and efficacy in the treatment of adults with Type 2 Diabetes Mellitus (T2DM).

DISCUSSION

Your questions are repeated below, followed by our preliminary responses sent to the sponsor on April 9, 2012, in bold font. The sponsor's responses, provided to FDA on April 12, 2012, follow in italics. The meeting discussion follows in bold italic font.

Clinical and Biostatistics

Question 1: Does the Agency agree that the proposed data pooling and analysis strategy for the Integrated Summary of Efficacy (ISE) provides appropriate information in the NDA for the Agency review of canagliflozin efficacy?

FDA Response: Yes, your proposed data pools are acceptable. Also show these data by individual study in a user-friendly and easily accessible format. For both the pooled data and the individual study data include a sensitivity analysis using the completers population.

In your demographics section as well as your renal subgroup analysis, you propose a renal cutpoint of $<60 \text{ mL/min/1.73m}^2$. Include an additional cutpoint of $<30 \text{ mL/min/1.73m}^2$.

Sponsor Response:

With regard to the request to perform a completer's analysis on the pooled population, the Sponsor proposes to provide such an analysis for the Moderate Chronic Renal Failure Pooled Population (which includes subjects across the Phase 3 program with baseline eGFR values of ≥ 30 to $< 60 \text{ mL/min/1.73 m}^2$), but not for the Placebo-controlled Study Population (which includes all canagliflozin or placebo treatment groups pooled from the 26 week Placebo-controlled studies), for the reasons discussed below.

Meeting Minutes
Type B, pre-NDA

The Moderate Chronic Renal Failure Pooled Population was specifically intended to evaluate overall efficacy of canagliflozin in subjects with moderate renal insufficiency in support of the results from the dedicated Phase 3 study, DIA3004 (subjects with baseline eGFR of 30 to < 50 mL/min/1.73 m²).

The Sponsor notes that each individual study report includes a completer's analysis for the primary endpoint (i.e., change from baseline in HbA_{1c}), in addition to the primary efficacy analysis using an LOCF approach (in mITT analysis set) and other supporting analyses including a per protocol analysis [which removes any non-completer's and subjects with protocol violations that may impact efficacy], and a mixed model analysis [as an additional sensitivity analysis].

The intent of the pooling of the placebo-controlled Phase 3, 26-week studies in creating the Placebo-controlled Study Population was to provide a more robust estimate of the glycemic response to canagliflozin within subgroups, and not to better assess overall efficacy response. The Sponsor believes that the subgroup analyses from the Phase 3 Placebo-controlled Population utilizing the primary mITT population with an LOCF approach is robust and should provide clarity on the impact of important subgroup factors. The Sponsor also notes that efficacy analyses in pre-specified subgroups (e.g., by age, sex, race/ethnic group, baseline HbA_{1c}, baseline eGFR, among other factors) was uniformly performed across individual studies (using the mITT population with an LOCF analysis) and provided in each study report (for subgroups meeting a minimum size of at least 60 subjects across all treatment groups combined).

Since the completer's analyses are provided within each study, and since the intent of the pooled analysis for the Placebo-controlled 26-week Phase 3 studies was to support subgroup analyses and not to provide an overall assessment of response, the Sponsor proposes not to include a completer's analysis on this pooled population.

The Sponsor will provide the additional baseline eGFR categorical summary of < 30 mL/min/1.73m² for both the pooled population of placebo-controlled Phase 3 studies and the pooled population of subjects with moderate renal impairment. It should be noted that all of the canagliflozin Phase 3 studies had exclusion criteria (or inclusion criteria in the case of the moderate renal impairment study, DIA3004) that did not allow subjects to be randomized if their pre-randomization visit (typically at Week-2) eGFR was < 30 mL/min/1.73m². As a consequence, there are only 21 subjects enrolled in the canagliflozin Phase 3 program that have a baseline eGFR < 30 mL/min/1.73m². (Note: Since the enrollment criteria were applied at Week -2, baseline (i.e., Day 1) values of eGFR were sometimes below screening values; hence a small number of subjects were randomized with baseline values below exclusion criteria cutpoint).

Meeting Discussion: The Agency found the sponsor's response acceptable.

Meeting Minutes
Type B, pre-NDA

Question 2: Does the Agency agree that the proposed data pooling and analysis strategy for the Integrated Summary of Safety (ISS) provides appropriate information in the NDA for the Agency review of canagliflozin safety?

FDA Response, Part 1: Your proposed data pools are acceptable. Pool #4 is the largest pool and includes the longest duration of follow-up.

It will be an important pool used for many of the adverse event analyses. For this pool, provide the tabular data organized by the following treatment groups:

Canagliflozin 100 mg
Canagliflozin 300 mg
All canagliflozin
Placebo
Active comparators
All comparators

Sponsor Response, Part 1:

For Datasets 3 and 4 (the Broad Population Dataset, and the Long-term/Exposure Broad Population Dataset, respectively; these datasets exclude DIA3015), the Sponsor has not analyzed the control groups (i.e., placebo or active comparator) separately, but only in a pooled fashion—combining the placebo and active comparator groups together to create the “non-canagliflozin” control group.*

As the table shows, the comparator agents (sitagliptin and glimepiride) come from 2 studies (DIA3006 and DIA3009), while the canagliflozin dose groups come from all 8 studies, and the placebo group comes from 7 studies. Comparison of results from the pooled active comparator treatment group to the pooled canagliflozin dose groups, would be comparing the adverse event experience in markedly different subject populations with different extents of exposure. The canagliflozin groups include a large number of subjects from DIA3008—the CV outcome study. This study includes an older population with substantial diabetic co-morbidities and diabetic microvascular complications, while the DIA3006 active comparator treatment group includes only arms from studies and DIA3009 which include populations that are younger, with lower incidences of diabetic complications and co-morbidities; moreover, the exposure to study drug for the DIA3008 is different from that of the DIA3009 or DIA3006 studies. Conclusions based upon comparisons of safety results from the pooled comparator group to results from the pooled canagliflozin groups would be comparing results from populations with different characteristics and different exposures to study drug be confounded.

To avoid this, the Sponsor has constructed the Dataset 3 and Dataset 4 comparison groups (canagliflozin 100 mg, canagliflozin 300 mg, pooled canagliflozin, and non-canagliflozin groups), with each study contributing comparably—with regard to type of subject (i.e., with regard to baseline characteristics) and subject exposure—to the non-canagliflozin group and to each of the canagliflozin dose groups.

Meeting Minutes
Type B, pre-NDA

Based upon this construction of the “non-canagliflozin” and each canagliflozin dose group (i.e., balanced contributions to the comparator and canagliflozin groups), Datasets 3 and 4 have highly similar baseline characteristics (demographic, anthropometric, and baseline diabetic characteristics) and highly similar exposure to study drug, indicating that these groups are appropriately balanced, and should support robust comparisons to assess safety and tolerability.

The Sponsor recognizes that pooling placebo with active agents creates a heterogeneous comparator population. Based upon this observation, the Sponsor has identified the pooled population from the 26-week placebo-controlled study population (that pools placebo and canagliflozin groups from studies DIA3002, DIA3005, DIA3006, and DIA3012) as the primary population to characterize safety and tolerability of canagliflozin. Nonetheless, the size and balanced characteristics/exposure of the comparison groups in Datasets 3 and 4, constructed as indicated above, will provide a highly useful and valuable analysis in support of safety and tolerability.

The Sponsor proposes to maintain the proposed pooling (canagliflozin 100 mg, canagliflozin 300 mg, combined canagliflozin groups, and pooled comparators) and not to provide the separate comparator groups (placebo, active control) as requested by the Agency.

Table 1. Studies with subjects contributing to Datasets 3 and 4

STUDY	Canagliflozin 100	Canagliflozin 300	Placebo	Glimepiride	Sitagliptin
DIA 3002 (n = 469)	X	X	X		
DIA 3005 (n = 584)	X	X	X		
DIA 3004 (n= 269)	X	X	X		
DIA 3006 (n = 1284)	X	X	X		X
DIA 3008 (n= 4327)	X	X	X		
DIA 3009 (n = 1450)	X	X		X	
DIA 3010 (n =714)	X	X	X		
DIA 3012 (n = 342)	X	X	X		

Meeting Discussion: *The sponsor provided clarification concerning pooled datasets to be included in the integrated summary of safety. A discussion pertaining to pooled dataset #4 and the value of presenting data for an ‘active comparator’ pool separately ensued. Since exposure data to active comparators will only be available for two out of eight studies, the sponsor expects that differences in baseline characteristics between the ‘canagliflozin’ pool and ‘active comparator’ pool would arise which would limit interpretability of observed differences.*

Meeting Minutes
Type B, pre-NDA

The Agency agreed that a pooled comparator population was not needed at the time of filing. The sponsor agreed to provide this data during the review process should the need arise.

The Agency stated that it would still be interested in pooled placebo-only comparisons for both datasets #3 and #4 since these represent the largest exposure in terms of number of subjects exposed and duration of exposure. Important variables susceptible to influence safety outcomes would in all likelihood be matched, mitigating interpretability issues, since the 'placebo' pool would be derived from seven out of eight total studies.

FDA Response, Part 2: In addition, analyses from this pool should be presented for all 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 for laboratory data. We do not agree with your proposal to provide blinded listings of adverse events that have occurred after each study's primary endpoint through the cut-off date for the NDA. These adverse events that have occurred during the extension periods should be included in the safety analyses and tabular analyses in the same way that events are being included that have occurred prior to the primary endpoint.

Sponsor Response, Part 2:

The Sponsor had constructed Dataset 3 (Broad Dataset) to include results through each Phase 3 study's primary time-point (Week 26 or 52) and through a specific cut-off date (September 15, 2011) for DIA3008 (since this study's primary endpoint is event driven, without a near term primary time-point). The rationale for this was to assure that all data included would be fully cleaned, emerging from a locked database from completed study phases. This is a substantial dataset with a mean subject exposure of 37 weeks and a total exposure of 9439 subjects (6742 subject years), including 6177 subjects (4468 subject years) exposed to canagliflozin and 3262 subjects (2274 subject years) exposed to placebo or comparator agents.

So as to assure that low frequency, but clinically important, events would be collected based upon a longer exposure, selected adverse events (i.e., fractures, venous thromboembolic events, selected neoplasms, photosensitivity adverse events, and events for renal or hepatic adjudication as well as MACE plus hospitalized unstable angina and hospitalized congestive heart failure) from the same pooled subject population of Dataset 3 were identified, cleaned, and included through end-January 2012 (and referred to as the Long-term exposure Broad Dataset – or Dataset 4). Since the Phase 3 studies were ongoing in extension periods, the safety results from this long-term extension Dataset (Dataset 4) would not be fully cleaned (other than the identified adverse events, noted above) or be based upon completed, locked databases. Based upon this, and the extensive exposure from Dataset 3, the Sponsor had proposed to include only focused safety results, as discussed above, from Dataset 4 in the NDA.

Meeting Minutes
Type B, pre-NDA

Based upon the Agency's request, the Sponsor will provide in the ISS analyses an overall summary of adverse event incidence, incidence of serious adverse event incidence (by SOC and preferred term), incidence of adverse events leading to discontinuation (by SOC and preferred term), deaths, and incidence of all specific adverse events (by SOC and preferred term) for Dataset 4. With regard to "adverse events of interest", the Sponsor proposes to focus on the adverse events of interest listed in bold above, which were pre-specified for evaluation in this Dataset.

The Sponsor notes that laboratory abnormalities reflecting important renal events and for hepatic events meeting pre-specified criteria that occurred through end-January 2012, across the canagliflozin program, were identified for adjudication (see response below for specific criteria); given the extensive safety laboratory results provided from Databases 1 through 3, and from the individual studies (including the large safety experience provided from the safety report from CANVAS), the Sponsor proposes not to include safety laboratory results from Database 4 in the NDA, but will provide updated analyses of abnormal laboratory results in the 4-month safety update.

The Sponsor notes that the analyses on Dataset 4 must be considered as preliminary, since the studies are ongoing, and data is subject to further cleaning prior to the database locks scheduled to occur once these extensions are completed. The final analyses will be included in the extension study reports that will be subsequently filed to the canagliflozin INDs.

Meeting Discussion: FDA found the response acceptable and agreed with the Sponsor's plan to provide updated analyses of abnormal laboratory results in the 4-month safety update.

FDA Response, Part 3: Clarify which adverse events were adjudicated, and whether the adjudication was prospective and blinded. Clarify if all events described in Section 6.6.12 of the ISS were adjudicated and whether there will be separate adjudication reports for these events or a summary of the adjudication findings. What specific information will be provided from the adjudication process?

Sponsor Response, Part 3:

The adjudication processes for each event were prospective and conducted by an external committee of individuals, with relevant experience and expertise that were blinded to treatment assignment. A tabular summary of the adjudication findings for all events described in section 6.6.12 (see below for specific outputs from each adjudication process) will be provided for these events within the ISS.

All adjudication charters and CVs for committee members will be included as an attachment to the ISS.

Events that are subject to adjudication, and are to be included in the NDA (for events occurring prior to January 31, 2012) include:

1. **Hepatic events** meeting the following criteria: *ALT or AST > 5X ULN or ALT or AST > 3 X ULN with a concomitant bilirubin > 2 X ULN. Causality association with study drug (definite, probable, possible, unlikely, excluded, not assessable) will be summarized. In addition a listing of liver injury type, severity and alternative etiologies, as assessed by the adjudication committee will be provided.*
2. **Renal events** meeting the following criteria: *a) doubling of serum creatinine over baseline that is sustained (for at least 4 weeks) or the last on study value, or b) a diagnosis of end stage renal disease (ESRD) or requiring renal replacement therapy (e.g. hemodialysis). Causality association with study drug (very likely, probable, possible, doubtful, not related) will be summarized. In addition a listing of alternative etiologies as assessed by the adjudication committee will be provided.*
3. **Fracture events:** *meeting the following criteria: All fractures from a pre-specified list of preferred terms. Type of fracture (categorized as low trauma, high trauma, pathologic, stress and other) and location of the fracture (categorized as lower limb; upper limb, pelvis, spine, thoracic cage, and skull/facial bone) will be summarized.*
4. **Cardiovascular events (MACE + unstable angina), venous thromboembolic events (deep venous thrombosis or pulmonary embolism) and hospitalized congestive heart failure:** *(investigator or sponsor identified events). Events confirmed by the committee will be summarized.*

Meeting Discussion:

Cases with hepatic events should be thoroughly worked-up and information pertaining to the work-up should be complete and available in the NDA. The Agency encouraged the sponsor to obtain all follow-up information for these cases and in particular results of diagnostic tests pointing to specific etiologies (e.g., auto-antibodies, imaging and viral serology for hepatitides including Hepatitis E).

FDA inquired whether endpoints other than the doubling of serum creatinine were considered in evaluating renal function across the canagliflozin program. The sponsor stated that they have performed and will include results of analyses for smaller clinically meaningful increases in serum creatinine (i.e., 50 % increase from baseline). FDA inquired whether creatinine assay (s) used for creatinine measurements were standardized (i.e., to the Isotope Dilution Mass Spectroscopy creatinine assay) across all trials in the program. Estimates of glomerular filtration rate may vary across standardized versus non standardized assays.

Meeting Minutes
Type B, pre-NDA

The sponsor confirmed that standardized creatinine assays were used across all the trial/regions in the program and that analyses and pooling were performed based on results from standardized assays.

FDA Response, Part 4:

In your ISS, include a section on hepatic events that includes the following:

- a. For the entire controlled phase 2/3 database (including the Japanese data and including the ongoing controlled extension trials), show the incidence of serum alanine aminotransferase (ALT) elevations >3x, >5x, >10x and >20x the upper limit of normal (ULN) for canagliflozin vs. non-canagliflozin treated patients. Include analyses that take into account patient-year exposure.**
- b. A query of your entire clinical database (phase 1-3 trials, including the Japanese data) for cases of biochemical Hy's Law (defined as serum ALT or AST >3x ULN and total bilirubin \geq 2x ULN).**
- c. Narratives for all cases of biochemical Hy's Law and all cases with serum ALT >10x ULN, regardless of whether the event was serious.**

Sponsor Response, Part 4:

The Sponsor will include a separate section of the ISS that presents results of hepatic safety analyses.

With regard to incidence of ALT or AST elevations, the Sponsor proposes to provide incidence tables of all transaminase elevations based upon the following cut-points pre-specified in the Statistical Analysis Plan for the ISS; for ALT and AST: > 3X, > 5X, and > 8X the ULN for canagliflozin versus non-canagliflozin subjects from the Dataset 3. In addition, the Sponsor will provide cut-points > 10X and > 20X from the same Dataset.

The pooled dataset (Dataset 3) contains laboratory results from all Phase 3 trials through the completed core periods (except DIA3015) and CANVAS through September 15, 2011. This dataset includes 6177 subjects treated with canagliflozin and 3262 subjects in comparator groups (placebo or active comparator). The Sponsor proposes to provide separate analyses from studies not included in Dataset 3 (i.e., Phase 2 studies and study DIA3015) in the ISS in the Section providing hepatic safety results. The Sponsor believes that the large subject exposure in the Dataset 3 will provide an extensive experience to support hepatic safety.*

With regard to events meeting the ALT/AST > 3X ULN and T Bili \geq 2X ULN criteria, all events across the entire clinical program (Phase 1 – 3 studies) with either an ALT or AST > 5X ULN or with a combined elevation of ALT/AST > 3X ULN and T Bili \geq 2X ULN were collected and were submitted for adjudication (see response above with regard to adjudication). Note that events through January 31, 2012 from all clinical studies were included in this analysis.

Meeting Minutes
Type B, pre-NDA

The results of the findings from the committee will be tabulated, including summary findings of all cases meeting criteria with an analysis that takes into account subject-year exposure.

The Sponsor will provide in the NDA the complete liver adjudication packages, including narratives, for all identified events with a serum ALT or AST > 5X ULN or with combined elevation of ALT/AST > 3X ULN and T Bili \geq 2X ULN.

Results of studies conducted by the Sponsor's Japanese partner (MTPC) utilize a separate database, to which the Sponsor does not have direct access, making pooling results from the Japanese studies with results from the Sponsor's studies not possible. In addition, the phase 3 studies being conducted by MTPC have minimal control subjects (1360 subjects randomized to canagliflozin doses and 80 to placebo). The Sponsor will obtain from MTPC all clinical cases meeting the criteria of ALT or AST > 3X ULN and T. Bili \geq 2X ULN for inclusion in the ISS. The Sponsor notes that there were no events meeting this criteria (or events with ALT > 3X ULN) in the Phase 1 or Phase 2b studies conducted by MTPC. The Phase 3 Japanese program is ongoing.

**Note: that DIA3015 was not included in the Dataset 3 or 4 as this study did not include both doses of canagliflozin (and hence would lead to imbalance in the construction of the comparison groups in this dataset). Renal and hepatic events from this study were screened for meeting renal or hepatic event adjudication criteria and adjudicated, as appropriate.*

Meeting Discussion: *The sponsor's response was found to be acceptable.*

Question 3: Does the Agency agree with the Sponsor's plan to provide only derived datasets that will support the safety analysis for selected events (for ISS Population 4) across the Phase 3 studies?

FDA Response: Clarify what you mean by derived datasets and what these datasets will contain. Include one dataset for your Pool #4 that contains all reported adverse events. Include another dataset for your Pool #4 that contains all laboratory data.

Sponsor Response:

In general, the analysis derived dataset contains the (a) raw data, (b) the treatment assignment, and (c) the analysis flags by which the submitted summary can be reproduced. The following derived datasets behind ISS Population 4 will be submitted.

Meeting Minutes
Type B, pre-NDA

Question 5: Further to the plan outlined in our 30 January 2012, communication (Serial No. 0355 for IND 76, 479) to provide the requested juvenile rat toxicology study in the 4- month safety update, does the Agency agree the label text regarding the effects of canagliflozin during fetal development may also be deferred to the 4-month safety update?

FDA Response: **Deferred submission of the juvenile rat study and associated labeling is acceptable.**

Sponsor Response: *No further discussion needed.*

Question 6: Does the Agency agree that providing the relevant electrocardiogram (ECG) Warehouse upload identification numbers in the NDA Reviewer's Guide is adequate for the Agency to access the thorough QT study ECGs from clinical study DIA1010?

FDA Response: **Your proposal is acceptable.**

Sponsor Response: *No further discussion needed.*

Question 7: Does the Agency agree with the plan not to provide a copy of the study protocols for the non-GLP preclinical studies?

FDA Response: **Yes. It is not necessary to include the study protocols for the non GLP pre-clinical studies, but a summary description of the methodology is expected in the study reports.**

SponsorResponse: *No further discussion needed.*

Question 8: Does the Agency agree with the proposed definitions of duration in the Study Tagging File (STF)?

FDA Response: **Yes.**

Sponsor Response: *No further discussion needed.*

Question 9: Does the Agency agree with the plan to submit tumor data from each rodent carcinogenicity study as an electronic dataset in SAS Transport (.xpt) file format created in Version 5 of SAS software, in accordance with FDA eCTD Study Data Specifications (Version 1.3, 27 Nov 2006)?

FDA Response: **Yes. We will contact you if difficulty is encountered with the submitted datasets. For more information on submitting electronic carcinogenicity data, please contact Karl Lin at karl.lin@fda.hhs.gov.**

Meeting Minutes
Type B, pre-NDA

Consider the following additional comments when preparing the non-clinical sections for NDA submission:

- **Include final study reports of the non-clinical studies. Draft reports will not be accepted.**
- **Histopathology sections should describe individual animal findings in addition to the summary tables, complete with incidence and severity scores.**
- **Summary toxicology tables are preferably separated by species and are accompanied by a listing of drug-related acute, sub-chronic, and chronic study findings, in-life observations, necropsy findings, and statistical notation where appropriate.**
- **Add a table that lists the drug batches used in non-clinical and clinical studies, including links to impurity profiles.**
- **Provide a summary table listing the area under the time-concentration curve (AUC) exposures to the two O-glucuronide metabolites, M5 and M7 in the pivotal toxicology studies.**
- **Clarify the status of the 15-month rat high fructose diet study (Protocol TXO10210).**

Sponsor Response: No further discussion needed.

Question 10: Does the Agency agree that the proposed content and eCTD format of the NDA, as outlined in the eCTD Content Outline and discussed in the pre-NDA Briefing Document are acceptable?

FDA Response: This is generally acceptable except where noted otherwise. Clarify how you plan to present the Japanese study reports and data. See our response to Question 14.

Sponsor Response: No further discussion needed. Refer to Sponsor response to Question 14.

Question 11: Does the Agency agree with the proposed list of covered studies to provide financial disclosure information for clinical investigators in the NDA?

FDA Response: No, you should submit financial disclosure information for study DIA3010, as well.

Sponsor Response: No further discussion needed.

Question 12: The Sponsor proposes to submit narratives and case report forms for all serious adverse events, deaths, and discontinuations due to adverse events. Does the Agency agree with this proposal?

FDA Response: We agree. In addition, provide narratives for selected hepatic events regardless of whether those events are serious (see our response under Question 2).

Meeting Minutes
Type B, pre-NDA

Ensure that all narratives are appropriately sorted and easily located via hyperlinks in the designated section of the ISS, and include hyperlinks for narratives in ISS Section 6.6.11 for “Selected Malignancies,” as well as Section 6.6.12.3 “Hepatic Events.” These links can launch the reviewer to a report with all the narratives consolidated together for that section, or there can be individual links that directly land the user on the pertinent patient narrative.

Sponsor Response: No further discussion needed.

Meeting Discussion: FDA clarified that for all relevant sections, hyperlinks should be used to direct the reviewer to the narrative. Narratives should be complete and summarize the clinical case history in written form.

Question 13: The Sponsor plans to submit published literature according to the following proposal:

The Sponsor will submit in Module 5, Section 5.4 copies of all published literature cited in Module 2.5, Clinical Overview and in Module 2.7, Clinical Summaries in accordance with the International Conference on Harmonization (ICH) guideline M4E. The Sponsor will perform a search of the published scientific literature for reports relevant to the clinical safety and effectiveness of canagliflozin using an appropriate cutoff date. Relevant published literature identified by the search will be summarized in a report to be included in Module 5, Section 5.3.5.4 copies of all relevant references will be provided in Module 5, Section 5.4.

References cited in the individual study reports will not be included in the submission but will be available upon request. Any other references that are not provided in Module 5 will be available upon request. Does the Agency agree with this approach?

FDA Response: This proposal appears acceptable.

Sponsor Response: No further discussion needed.

Question 14: Does the Agency agree with the proposal for providing study reports for completed nonclinical and clinical studies conducted by the Sponsor’s collaboration partner, Mitsubishi Tanabe Pharma Corporation (MTPC)?

FDA Response: Clarify how you plan to present these Japanese data. A summary of the pooled Japanese safety data should be presented in the body of the ISS in both text and tabular form. This should include analyses of deaths, serious adverse events, discontinuations due to adverse events, bone safety and the selected malignancies. Hepatic events should be included in the liver analysis requested in our response to Question 2.

Sponsor Response: The clinical development program sponsored by MTPC (shown in the table below) is ongoing.

Meeting Minutes
Type B, pre-NDA

As such, the only completed clinical trials are three phase 1 studies and one phase 2 trial. The MTPC phase 3 program has been initiated but it is not anticipated that clinical study reports will be available during the NDA review cycle. As presented in the Sponsor's EOP2 background document, the Sponsor will provide translated clinical study reports from all completed MTPC studies and this data will not be integrated with the Sponsor's data in the CANA NDA. Safety tables from the completed phase 2 study will be included in the ISS. With regards to the pooling of the Japanese data, please refer to the Sponsor's response to question 2.

Meeting Discussion: Sponsor's response was found to be acceptable.

COMPLETED AND ONGOING MITSUBISHI TANABE (MTPC) STUDIES

Study ID Study Status	Phase Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment
(b) (4)			

Meeting Minutes
Type B, pre-NDA

Study ID Study Status	Phase Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment
(b) (4)			

Meeting Minutes
Type B, pre-NDA

Study ID Study Status	Phase Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment
	(b) (4)		

Question 15: For the early clinical studies in exploratory development (designated as “NAP” studies), the Sponsor proposes to provide the analysis datasets in a legacy format that is different than the format that will be used for the clinical studies in Phase 1 or late development (Phase 2 and 3). The legacy format datasets will meet the required electronic submission standards. Does the Agency agree with this proposal?

FDA Response: This is acceptable.

Sponsor Response: No further discussion needed.

Additional FDA Comments:

Clinical Pharmacology:

- Follow-up pertaining to our advice from September 23, 2011: Include the canagliflozin formulation used in the phase 3 clinical trials (b) (4) as a covariate in your population pharmacokinetic analysis.**

Sponsor Response: No further discussion needed.

Clinical:

- Although canagliflozin’s mechanism of action is dependent on renal function, patients with severe renal impairment may be prescribed canagliflozin, or patients with moderate renal impairment may experience worsening renal function while taking canagliflozin. Clarify whether you plan to study efficacy and safety in patients with severe renal impairment.**

Sponsor Response: The Sponsor anticipated that reduced glycemic efficacy would be seen in subjects with moderate chronic renal insufficiency, relative to subjects with normal (or mildly impaired) renal function, since urinary glucose excretion is directly proportional to the glomerular filtration rate (and to ambient plasma glucose concentrations). The Sponsor completed a dedicated study in T2DM subjects with moderate renal insufficiency (DIA3004, subjects eGFR 30 - < 50 mL/min/1.73 m²) and in this study, and in the pre-specified cross Phase 3 pooled moderate chronic renal failure population (subjects with eGFR 30 - < 60 mL/min/1.73 m²), presented in the Integrated Summary of Efficacy, showed clinically useful and statistically significant reductions in HbA_{1c}.

However, these reductions were attenuated (~50%) relative to reductions in HbA_{1c} seen in the Phase 3 studies in T2DM populations with normal or only mildly impaired renal function (e.g., eGFR > 50 mL/min/1.73 m²).

Based upon this observation, and the even further reduced UGE (from the Phase 1 study DIA1003 in individuals with varying severity of renal insufficiency) that is seen in subjects whose eGFR is < 30 mL/min/1.73 m², the Sponsor would not expect meaningful efficacy and hence is not planning to conduct studies in these latter subjects with severe renal insufficiency. The Sponsor will include information in the proposed prescribing information regarding attenuation of efficacy based upon renal function.

Meeting Discussion: *The response was found to be acceptable. The determination whether a study in a patient population with severe renal insufficiency will or will not be required will be made after review of the submitted data.*

- 2. For the CANVAS insulin sub-study, you plan on submitting primary efficacy analyses for patients using >30 units of insulin per day but the study enrolled patients who were using >20 units per day. Clarify why all insulin-treated patients are not being included in the primary efficacy analysis.**

Sponsor Response: During the initiation of the CANVAS study, feedback from EMA was received (Procedure No; EMEA/H/SA/1252/1/FU/2009/II), suggesting that the selected minimum dose for insulin (≥ 20 units/day) might be considered as relatively low, and not fully consistent with evidence of sufficient up-titration. To address this feedback, the Sponsor pre-specified in the insulin substudy statistical analysis plan that while subjects with the originally required insulin dose (≥ 20 units/day) will be evaluated, the primary efficacy analysis would focus on subjects who were on a higher minimum dose (≥ 30 units/day). The rationale for this approach was to provide consistent information to physicians globally. Since approximately 83% of randomized subjects in the insulin substudy were taking ≥ 30 units/day, the profile of this population was unlikely to meaningfully differ from the profile of subjects on at least 20 units/day. Since the protocol-specified minimum dose was 20 units/day, the initial hypothesis testing evaluated the primary hypothesis (HbA_{1c}-lowering relative to placebo) and the key secondary hypotheses (testing each dose for body weight loss, FPG, and proportion with HbA_{1c} < 7%) in Population 1 (i.e., subjects on at least 20 units/day). After demonstrating statistical significance for all of these hierarchically examined hypotheses, the evaluation of Population 2 proceeded. Thus, the primary efficacy endpoint and major secondary endpoint analyses were performed in Population 1 (subjects on at least 20 units/day) which served as a gatekeeper to Population 2 (subjects on at least 30 units/day).

Meeting Minutes
Type B, pre-NDA

As noted above, to avoid characterizing 2 different add-on to insulin populations (with 2 different profiles, even if minimally different), for both the U.S. NDA and EMA/ROW submissions, Population 2 will serve as the primary population. Similarly, safety analyses will focus on Population 2 (key safety tables will be generated for Population 1 as a supportive analysis, and any differences from conclusions based upon Population 2 will be noted in the insulin substudy CSR).

Meeting Discussion: *The sponsor's response was found to be acceptable.*

- 3. Clarify how you will be presenting the cardiovascular safety results. Include data on length of patient exposure to study medication in the meta-analysis and in CANVAS. These data should include the number of patients in the meta-analysis and in CANVAS who were exposed to study medication for at least 6 months and for at least 1 year.**

Sponsor's Response: The CV meta-analysis to demonstrate CV safety will be included in the ISS. The CV meta-analysis population includes Phase 2 and 3 studies in T2DM of \geq 12 weeks duration.

An analysis of the hazard ratio and 95% CI for MACE+ will be presented for:

- Overall meta-analysis population
- CANVAS alone
- Non-CANVAS studies pooled
- By Dose
- By components of the MACE+
- By pre-specified subgroups

Exposure to study drug (i.e. \geq 26 weeks to $<$ 52 weeks and \geq 52weeks) will be summarized:

- Overall meta-analysis population
- CANVAS

Meeting Discussion: *The sponsor's response was found to be acceptable.*

The FDA asked for clarification regarding the recent decision to unblind the CANVAS trial. In particular the sponsor was asked to discuss how this decision would impact the planned enrollment for cohort B, and the plan to carry out a new dedicated CV outcomes study designed to show CV benefit. The company explained that the decision to unblind CANVAS without seeking Agency input was made after elevations in LDL were discovered. The sponsor felt that having unblinded results would facilitate internal company decision making and that public release of this information would be useful to potential prescribers.

- 4. Ensure all laboratory data are in U.S. units.**

Meeting Minutes
Type B, pre-NDA

Sponsor Response: The laboratory data units will be presented in both SI and Conventional (U.S. units) in the text and/or attachments.

Meeting Discussion: None

- 5. Clarify how you intend to present new data in the four-month Safety Update. We do not agree with showing new data only in line listings as that is not a user friendly approach for review. In addition, in Section 14.6 (page 42) you state that drug-related adverse events leading to discontinuation will be included in the four-month Safety Update.**

The Safety Update should include all adverse events leading to discontinuation, regardless of the investigator or sponsor attribution of causality.

Sponsor Response: As requested by the Agency, the Sponsor will provide tabulations by treatment group (canagliflozin 100mg, canagliflozin 300mg, total canagliflozin and non-canagliflozin group), for SAEs (including deaths), AEs leading to discontinuation regardless of attribution.

Meeting Discussion: This is acceptable.

- 6. For discontinuations due to “other”, provide further information as to the reasons within this category that led to discontinuation and clarify whether any discontinuations due to adverse events or inadequate efficacy were inadvertently categorized as “other”.**

Sponsor Response: The Sponsor will submit details of discontinuation due to “other” as requested.

Meeting Discussion: This is acceptable.

POST-MEETING STATISTICAL COMMENTS:

In addition to the discussion of the interim unblinding of the CANVAS A study at the pre-NDA meeting on 4/13/12, we refer to the letter of February 29, 2012 (submitted under 0374), (b) (4)

We request that you provide the following:

- 1.** (b) (4)

Meeting Minutes
Type B, pre-NDA

(b) (4)

ADDITIONAL CLARIFICATIONS REQUESTED FROM OSI

The Sponsor seeks clarification (*in italics*) on the items noted below from the Office of Scientific Investigations.

I. Request for general study related information and specific Clinical Investigator Information

d. Current Location of Principal Investigator (if no longer at Site): Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email)

Sponsor Question: Is OSI seeking contact information for Principal Investigator(s) who were at a site and enrolled subjects at that site, but the Principal Investigator subsequently leaves the site?

OSI Response: Yes. OSI suggests including both original site contact information and updated PI contact information (if necessary).

Follow-up Clarification from Sponsor: The Sponsor proposes to provide all the contact information for the original PI under one Variable [ORPI] rather than under separate variables.

Meeting Minutes
Type B, pre-NDA

The rationale for this is that the current PI information will be contained in the standard variable list provided by the Agency and the Sponsor does not want to over-ride this information.

OSI Response: *This is acceptable.*

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For the primary endpoint “change from baseline to Week 26 or 52 in HbA1C”, provide the data listings used to generate the calculated endpoint (i.e. the baseline value and all protocol specified values of HbA1C.

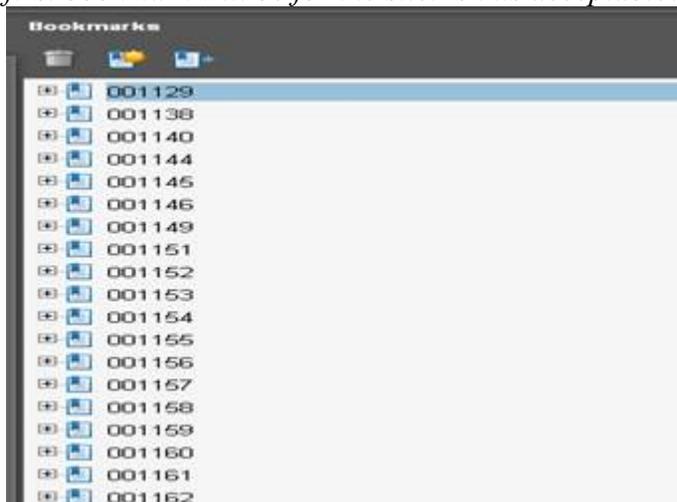
j. By subject listing, of laboratory tests performed for safety monitoring

Follow-up Clarification from Sponsor: We will provide the listing of the primary and secondary endpoint efficacy parameters or events as requested for 1h. For request 1j, the Sponsor proposes to provide the following LAB tests for the PDLC analysis: Albumin, ALT, AST, Bilirubin, Bicarbonate, Calcium, Creatinine Kinase, eGFR, Magnesium, Phosphorus, Potassium, Sodium, Uric Acid, Hemoglobin, Platelets, White Blood Count. Is this acceptable?

OSI Response: *This is acceptable.*

2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:

Sponsor Question: The Sponsor is unable to provide a bookmark for the field: Study # X. The first bookmark will be for the site. Is this acceptable?



Meeting Minutes
Type B, pre-NDA

OSI Response: *It appears from the diagram above that these folders are arranged by study and the sites are within the study folder. If this is the case, then this is acceptable.*

III. Request for Site Level Dataset

The Define file for the dataset is presented in Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE).

Follow-up Clarification from Sponsor: *We would like concurrence from the Agency with our proposals below regarding specific clinical site data elements to be included the listings.*

1. *For the Variable Index 27 and 28- FINLMAX and FINLDISC the sponsor proposes to provide A YES/NO entry rather than an actual amount. Is this acceptable?*

OSI Response: *OSI prefers the actual amount but a YES/NO is acceptable.*

2. *For the Variable Index 35- COUNTRY, the sponsor proposes to provide 3 digit codes to be compliant with SDTM controlled terminology. Is this acceptable?*

OSI Response: *Yes, this is acceptable.*

3. *The Sponsor proposes to add in a variable: ROLE to distinguish principal investigator and sub-investigators. Is this acceptable?*

OSI Response: *OSI is requesting only the principal investigator information in investigator's variable indexes of the site-level dataset. There is no need to add the variable ROLE to distinguish between the principal investigator and the sub-investigator.*

JRD would like respectfully ask the Office of Scientific Investigations (OSI) and the Division of Metabolism & Endocrinology Products if we can submit the information requested by OSI (as per the Agency preliminary feedback dated 9 April 2012) 30 days post our NDA filing to the OSI/ Agency. We appreciate all of the clarifications that that OSI has provided thus far and we are diligently putting together the requested information.

OSI Response: *OSI strongly recommends that the responses to Part I (general information) and Part III (Site Level Data Sets for the "risk based model for site selection") of our request be provided with the NDA at the time of filing. It is acceptable to submit the responses to Part II (Subject Level Data Listings by Site) thirty days after filing.*

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

/s/

JENA M WEBER
06/13/2012



NDA 204042

NDA ACKNOWLEDGMENT

Janssen Research & Development LLC
Attention: Sukhdev Saran
Associate Director, Regulatory Affairs
920 U.S. Highway; P.O. Box 300
Raritan, NJ 08869

Dear Ms. Saran:

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

Name of Drug Product: Canagliflozin 100 mg and 300 mg Oral Tablets

Date of Application: May 31, 2012

Date of Receipt: May 31, 2012

Our Reference Number: NDA 204042

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **July 30, 2012**, in accordance with 21 CFR 314.101(a).

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

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena M. Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JENA M WEBER
06/05/2012



NDA 204042

NDA ACKNOWLEDGMENT

Janssen Research & Development LLC
Attention: Sukhdev Saran
Associate Director, Regulatory Affairs
920 U.S. Highway; P.O. Box 300
Raritan, NJ 08869

Dear Ms. Saran:

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

Name of Drug Product: Canagliflozin 100 mg and 300 mg Oral Tablets

Date of Application: May 31, 2012

Date of Receipt: May 31, 2012

Our Reference Number: NDA 204042

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If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena M. Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JENA M WEBER
06/04/2012



IND 076479

ADVICE/INFORMATION REQUEST

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

Dear Ms. Saran:

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

We also refer to your amendment dated December 20, 2011, requesting deferral from providing pediatric data as required by the Pediatric Research Equity Act (PREA), until positive risk/benefit has been established in adults.

We have reviewed your submission and have the following comments and recommendations:

A request for a partial waiver in patients less than 10 years of age, and a deferral in patients 10 to less than 17 years of age, is consistent with our current approach to new non-insulin anti-diabetic medications. However, please be aware that all deferral, waiver, and partial waiver decisions are not finalized until your request is presented before the Pediatric Review Committee (PeRC) during the review process of your NDA.

We concur that the study of canagliflozin in pediatric patients should not be initiated until there is adequate evidence of efficacy and safety in adults. We recommend that you prepare your non-clinical and clinical pediatric program while your development proceeds in adults.

All deferral, waiver, and partial waiver requests that will be submitted to your NDA must include justification and supporting rationale with documentation. In addition, as stated in section 505B of the Federal Food Drug and Cosmetic Act, a deferral request must contain a pediatric plan. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy), sufficient to demonstrate dose, safety, and efficacy.

For additional information, please see the *Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act*:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening adverse experiences associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];
- Reporting any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, in writing to this Division and to all investigators within 15 calendar days after initial receipt of this information [21 CFR 312.32(c)(1)]; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, 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

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

/s/

MARY H PARKS
02/15/2012



IND 76,479

REVISED MEETING MINUTES

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

Dear Ms. Saran:

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

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on April 28, 2009, and to the meeting minutes issued on June 25, 2009.

We acknowledge an error in the summary of the meeting discussion under Question 1A. The following statement in the June 25, 2009, meeting minutes is incorrect:

[REDACTED] (b) (4)

The meeting minutes have been corrected to state [REDACTED] (b) (4)

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

Sincerely,

{See appended electronic signature page}

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

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



MEMORANDUM OF MEETING MINUTES

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

MEETING CHAIR: Mary Parks, MD

MEETING RECORDER: Julie Marchick, MPH

FDA ATTENDEES:

Division of Metabolism and Endocrinology Products

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

Office of Biostatistics

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

Office of Clinical Pharmacology

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

EXTERNAL CONSTITUENT ATTENDEES:

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

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

BACKGROUND:

IND 76,479 for JNJ-28431754 Oral was submitted by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. on April 25, 2007. JNJ-28431754 is a sodium-glucose co-transporter (SGLT2) inhibitor being studied for the treatment of type 2 diabetes mellitus (T2DM). (b) (4)

Proposed Phase 3 Clinical Program

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

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

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

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

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

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

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

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

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

MEETING OBJECTIVES:

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

DISCUSSION POINTS:

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

Cardiovascular Outcomes Trial

Question 1: Statistical Analysis

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

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

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

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

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

(b) (4)

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

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

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

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

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

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

Response: See response to Question 1B.

Meeting Discussion: See discussion under Question 1B.

Question 2: Glycemic Control Analysis in Sub-Studies

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

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

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

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

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

Meeting Discussion: None

Question 3: Stratification

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

Response: Yes

Meeting Discussion: None

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

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

Response: See response to Question 1B

Meeting Discussion: None

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

Response: See response to Question 1B.

Meeting Discussion: None

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

Response: Yes

Meeting Discussion: None

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

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

Meeting Discussion: None

Question 5: Collection of Adverse Events

Does the Agency agree with the proposal to analyze, in accordance with the FDA Critical Path Initiative, only serious adverse events, non-serious adverse events causing study drug

discontinuation, and predefined adverse events of special interest for the post-NDA approval Phase of the CV outcomes trial?

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

Meeting Discussion: None

Question 6: Reporting of Adverse Events

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

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

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

Meeting Discussion: None

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

Question 7: Reduction of Renal Risk

A secondary objective of the CV outcomes trial [REDACTED] (b) (4)

[REDACTED] Does the Agency agree that this analysis will, if successful, [REDACTED] (b) (4)

[REDACTED] (b) (4)

Response: The Division does not agree. What the Sponsor is proposing is not considered a [REDACTED] (b) (4)

[REDACTED]

(b) (4)

Meeting Discussion: The Sponsor asked whether it would be useful for prescribers to know from the label whether patients progress to (b) (4). The Division stated that the Sponsor should submit a proposal, which the Division will discuss with the Cardio-Renal Division.

Safety

Question 8: Renal Safety

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

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

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

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

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

Obtaining safety data with the 300 mg dose in patients with moderate renal impairment is encouraged because some patients with moderate renal impairment are likely to be inadvertently exposed to the 300 mg dose of the product, if approved, if a healthcare provider relies only on serum creatinine as an estimate of renal function or if renal function deteriorates between clinic visits.

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

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

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

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

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

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

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

Meeting Discussion: None

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

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

Meeting Discussion: None

Question 9: Bone Safety

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

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

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

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

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

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

Question 10: Evaluation of Photosensitivity Potential

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

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

Meeting Discussion: None

Question 11: Hypoglycemia

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

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

Meeting Discussion: None

Efficacy

Question 12: Comparison to Sitagliptin

Does the Agency agree that the designs of the two proposed studies (DIA3006 and DIA3002) to assess the superiority of JNJ-28431754 to sitagliptin on glycemic control and bodyweight are appropriate and pending results the data could be included (b) (4) ?

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

Meeting Discussion: None

Question 13: Study "Run-in" Period

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

Response: Yes.

Meeting Discussion: None

Statistics

Question 14: Subgroup Analyses

Does the Agency agree that data from the proposed meta-analyses of change in blood pressure and HbA1c for all subjects across Phase 3 glycemic assessment studies and also within predefined subgroups of subjects with high baseline blood pressure and HbA1c will provide sufficient data for inclusion of the subgroup analysis results [REDACTED] (b) (4) [REDACTED] ?

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

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

Question 15: Operational Plan for Study Extension

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

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

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

Meeting Discussion: None

Question 16: Phase 3 Clinical Program

Does the Agency concur that the studies included in the proposed Phase 3 clinical development program through their respective primary endpoint durations comprise a complete package with adequate exposures to characterize the benefit/risk ratio in support of

a New Drug Application filing of oral immediate-release JNJ-28431754 for the proposed indication and proposed USPI?

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

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

Question 17: Target Population

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

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

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

Question 18: Secondary Endpoints

The Phase 3 glycemic efficacy studies will have clinically relevant pre-specified secondary endpoints (e.g. change in weight, FPG). A hierarchical testing procedure will be developed to test the treatment differences (JNJ-28431754 vs. control) for the primary and secondary endpoints in each study to preserve the overall type 1 error rate. Does the Agency agree that these secondary endpoints pending results will provide sufficient data for inclusion (b) (4) ?

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

Meeting Discussion: None

Clinical Pharmacokinetic and Pharmacology

Question 19: Drug-Drug Interaction Study

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

Response: No, the Division does not agree.

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

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

Meeting Discussion: None

Question 20: Food Effect – BA-BE Study

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

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

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

Study 2843175NAP1003 has the following issues:

Food Effect Guidance's Recommendation

The highest strength of a drug product intended to be marketed should be tested.

A high-fat and high-calorie meal is recommended as a test meal.

Fasting should be an overnight fast of at least 10 hours. No food should be allowed for at least 4 hours post-dose.

Following an overnight fast of at least 10 hours, participants should receive the dose right after the test meal.

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

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

Meeting Discussion: None

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

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

Meeting Discussion: None

Nonclinical

Question 21: Metabolite Characterization

The major metabolic elimination pathway for the compound in humans is *O*-glucuronidation. The two major human plasma circulating metabolites M5 and M7 (two *O*-glucuronide

Study 2843175NAP1003's Design

The highest strength tested for food effect was the 200 mg JNJ-28431754 Phase 2 tablet formulation, whereas the highest to-be-marketed strength will be the 300 mg JNJ-28431754 tablet formulation.

No information on the meal content.

No information on the condition of fast for the participants who received the single 25 and 200 mg tablets. The fasted participants who received the 400 mg dose (2 x 200 mg tablets) received breakfast 30 minutes after dosing.

Participants received the 25, 200, and 2 x 200 mg tablets 10 minutes before the breakfast.

conjugates of the parent) were not quantitatively measured in GLP toxicology studies. For pharmacokinetic characterization both metabolites were measured in humans at selected doses in different clinical studies.

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

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

Meeting Discussion: None

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

Response: The Division agrees.

Meeting Discussion: None

Question 22: Clinical Pharmacology and Pharmacokinetic Studies

Does the Agency agree that the completed clinical pharmacology and pharmacokinetics studies are sufficient to support the initiation of the proposed Phase 3 studies and that the completed, ongoing and planned clinical pharmacology pharmacokinetics studies comprise a complete package in support of Drug Application filing of oral immediate-release JNJ-28431754 for the proposed indication (b) (4)

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

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

The Sponsor should address JNJ-28431754's enterohepatic recycling potential, since JNJ-28431754 is extensively metabolized to the M5 and M7 glucuronides which can

undergo enterohepatic recycling in humans. Disruption of the enterohepatic recycling such as antibiotic coadministration may decrease systemic JNJ-28431754 exposure and cause efficacy concern.

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

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

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

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

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

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

Post-Meeting Comment:

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

- *The clinical multiple-dose DDI studies may involve the complex interplay of JNJ-28431754, M5, and M7 with UGT isozymes, CYP isozymes and transporters, which makes the interpretation of individual M5 and M7's CYP isozymes induction potential difficult.*
- *JNJ-28431754's major metabolism is via glucuronidation. If auto-induction were to occur then it should be the UGT isozymes' auto-induction rather than the CYP isozymes' auto-induction, which is not relevant.*
- *The Sponsor indicated (Meeting Package's page 16 and pre-Meeting April 27, 2009 response above) that Study FK6320 examined up to 4.4 μ g/mL (10 μ M) JNJ-28431754.*

Per the renal impairment study (28431754-DIA-1003), mean plasma JNJ-28431754 C_{max} is 1.475 $\mu\text{g/mL}$ upon an oral single 200 mg dose administration to healthy participants. The mean plasma JNJ-28431754 C_{max} upon the proposed oral 300 mg once daily dose administration will be higher than 1.475 $\mu\text{g/mL}$ due to the higher dose and accumulation (mean $t_{1/2}$ = 17.4 h). Thus, Study FK6320 might not have examined a high enough JNJ-28431754 concentration to address JNJ-28431754's CYP induction potential in vitro.

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

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

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

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

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

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

Post Meeting Comments:

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

Because JNJ-28431754 has (b) (4), the Sponsor should address whether JNJ-28431754 shows any (b) (4) via metabolism in humans.

Question 23: Non-Clinical Studies

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

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

Meeting Discussion: None

(b) (4)

Pediatric

Question 26: Submission of Pediatric Data

The Sponsor intends to submit a Proposed Pediatric Study Request (PPSR) [REDACTED] (b) (4)

[REDACTED] Does the Agency concur with the proposal to defer submission of pediatric data, as required by the Pediatric Research Equity Act (PREA), for JNJ-28431754 as a treatment for T2DM mellitus until after a favorable benefit/risk in adults has been established at NDA approval?

Response: See the response to Question 27.

Meeting Discussion: See Meeting Discussion under Question 27.

Question 27: Partial Waiver

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

Response (Questions 26 and 27): The request is reasonable. However, formal request for deferral and waiver with an accompanying rationale must be included in the NDA

together with a proposed pediatric plan (e.g., synopses of proposed pediatric trials). This plan should include a timeline proposing when the finalized pediatric protocol(s) will be submitted to FDA, when the proposed pediatric trial(s) will start, and when the completed clinical study report(s) will be submitted to FDA. A final decision regarding the requested deferral and waiver cannot be made until the Division discusses this request with the Pediatric Review Committee (PeRC) after we have completed review of the NDA.

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

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

Question 28: PREA Study Proposals

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

(b) (4)

Response: It is premature to discuss the design of the pediatric study at this time. See response under Question 26.

(b) (4)

:

(b) (4)

Meeting Discussion: None

Mechanism of Action

Question 29: SGLT1 Effect

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

Response: This will be a review issue.

Meeting Discussion: None

Question 30: [redacted] (b) (4)

[redacted] (b) (4)

Response: No, this would not be sufficient.

[redacted] (b) (4)

[redacted]

[redacted]

Meeting Discussion: None

Additional Comments:

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

Meeting Discussion: The Sponsor presented slides and explained their rationale for selecting the 100 mg and 300 mg doses.

In addition, the Sponsor stated that the safety and tolerability of the 50 mg dose is equivalent to that of the 100 mg dose based on the available data to date. The Division stated that studying the 100 mg and 300 mg doses is acceptable but recommended that the Sponsor consider studying the 50 mg dose in some phase 3 trials in case a safety concern arises with the higher doses.

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

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

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

Meeting Discussion: None

- 4. In some trials, the Sponsor is discontinuing patients who require glycemic rescue therapy. The Division recommends that these patients initiate glycemic rescue but**

remain in the trials to bolster the safety database. Safety analyses can be performed in two ways: prior to rescue and regardless of rescue. For efficacy analyses, measurements after glycemic rescue can be considered missing.

Meeting Discussion: None

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

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

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

Meeting Discussion: None

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

Meeting Discussion: The Sponsor acknowledged the typographical error.

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

Meeting Discussion: None

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

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

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

Meeting Discussion: None

Additional Discussion Topic

SGLT2-Associated Pulmonary Embolus

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

ATTACHMENT:

Slides presented by Sponsor during the meeting

Minutes Preparer: Julie Marchick

Chair Concurrence: Mary Parks

Linked Applications

Sponsor Name

Drug Name / Subject

IND 76479

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/s/

JULIE C MARCHICK
07/13/2009