CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s000

<u>OTHER REVIEW(S)</u>

RPM FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA 204042	NDA Supplement: N/A	Efficacy Supplement Type SE- 1
Proprietary Name: Invokana Established/Proper Name: canagliflozin Dosage Form: Tablets Strengths: 100 and 300 mg		
Applicant: Janssen Research & Development, LLC Agent for Applicant (if applicable): N/A		
Date of Application: May 31, 2012 Date of Receipt: May 31, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: **March 31, 2013**	Action Goal Date: **March 29, 2013**	
Filing Date: July 30, 2012	Date of Filing Meeting: July 31, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication: As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus.		
Type of Original NDA: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	505(b)(1) N/A	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	Standard	
Resubmission after withdrawal? No	Resubmission after refuse to file? No	
Part 3 Combination Product? No	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC **Other: None**	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number: 076479

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system?	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:			✓	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status	Payment for this application: Paid (PD3012205) $1,841,500.00

If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Not in arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			✓	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**			✓	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			✓	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			✓	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		✓		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**?		✓		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **Yes, requested 5 years of exclusivity**	✓			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?			✓	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	All electronic eCTD			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only)	✓			Legible, English, pagination, avigable hyperlinks
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].***	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge…"*	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?	✓			

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?			✓	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***Note**: All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			**Meeting held 3/13/13**
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	✓			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?	✓			Waiver & Deferral requested. Pediatric Plan included in submission.
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	✓			314.55(b) 314.55(c)
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request?		✓		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	✓			Acceptable
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		✓		Will not have a REMS.
Prescription Labeling				
Check all types of labeling submitted.	Package Insert, Patient Information Med Guide Carton & container labels			

	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	✓			
Is the PI submitted in PLR format?[2]	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request?			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			PI, PPI, C & C,
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓		✓	N/A as of filing
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	**Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
If representative labeling is submitted, are all represented SKUs defined?				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed?	✓			CDRP: 10/25/12 (renal); OSE: 10/25/12 (liver); DRUP: 10/25/12 (bone.

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting **Date: 4/28/09**	✓			
Pre-NDA Meeting **Date:** 4/13/12 ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date: 3/18/08 (PCL)**	✓			

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 31, 2012

NDA: 204042

PROPRIETARY NAME: Invokana

ESTABLISHED/PROPER NAME: canagliflozin

DOSAGE FORM/STRENGTH: 100 & 300 mg Tablets (for oral use)

APPLICANT: Janssen Research & Development, LLC

PROPOSED INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus.

BACKGROUND: NME. A sodium-glucose co-transporter 2 (SGLT2) inhibitor

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jena Weber	Yes
	CPMS/TL:	Julie Marchick	Yes
Cross-Discipline Team Leader (CDTL)	Jean-Marc Guettier		Yes
Clinical	Reviewer:	Hyon Kwon	Yes
	TL:	Jean-Marc Guettier	Yes
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:		N/A
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:		N/A
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	N/A
	TL:		N/A

Clinical Pharmacology	Reviewer:	Jaya Vaidyanathan Manoj Khurana	Yes Yes
	TL:	Lokesh Jain Immo Zadezensky	No Yes
Biostatistics	Reviewer:	Eugenio Andraca-Carrera Wei Liu	Yes Yes
	TL:	Mat Soukup Aloka Chakravarty Todd Sahlroot	No Yes Yes
Nonclinical (Pharmacology/Toxicology) Teritary (Paul Brown)	Reviewer:	Fred Alavi Dan Minck Paul Brown	Yes Yes No
	TL:	Todd Bourcier	Yes
Statistics (carcinogenicity)	Reviewer:	Min Min	No
	TL:	Karl Lin	No
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Sheldon Markofsky	Yes
	TL:	Su Tran Danae Christodoulou	Yes No
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	N/A
	TL:	N/A	N/A
CMC Labeling Review	Reviewer:	Shelly Markofsky	Yes
	TL:	Su Tran Ali Al Hakim	Yes Yes
Facility Review/Inspection	Reviewer:	To be scheduled. Facility(ies) information submitted	No
	TL:	Danae Christodoulou	No
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin Yelena Maslov Riata Toss	No No Yes
	TL:	Yelena Maslov	No
OSE/DRISK (REMS)	Reviewer:		
	TL:		

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	N/A	N/A
	TL:		N/A
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
ONDQA Biopharmaceutics	Reviewer: Houda Mahayni TL: John Duan TL: Angelica Dorantes		Yes No Yes
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues?	Not Applicable
• Per reviewers, are all parts in English or English translation?	YES
• Electronic Submission comments	None
CLINICAL **Comments**: Additional requests for 74-day letter.	FILE
• Clinical study site(s) inspections(s) needed?	YES
• Advisory Committee Meeting needed? **Comments**:	YES Date if known: January 10, 2013
• Abuse Liability/Potential **Comments**:	Not Applicable
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	Not Applicable
CLINICAL MICROBIOLOGY	Not Applicable

CLINICAL PHARMACOLOGY **Comments**:	FILE
• Clinical pharmacology study site(s) inspections(s) needed?	NO
BIOSTATISTICS **Comments**:	FILE
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	FILE

IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	Not Applicable
PRODUCT QUALITY (CMC) **Comments**:	FILE
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	YES
Quality Microbiology (for sterile products)	Not Applicable

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	YES YES
Facility/Microbiology Review (BLAs only)	Not Applicable
CMC Labeling Review **Comments**: None at this time	N/A

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Curtis Rosebraugh, M.D. Office Director (ODE II)

	REGULATORY CONCLUSIONS/DEFICIENCIES
	The application is unsuitable for filing. Explain why:
✓	The application, on its face, appears to be suitable for filing. Review Issues: No review issues have been identified for the 74-day letter. Some comments & requests only. Review Classification: Standard Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 204042

Name of Drug: Invokana (canagliflozin) 100 mg and 300 mg Tablets

Applicant: Janssen Research & Development

Labeling Reviewed

Submission Date: March 29, 2013 (final)

Receipt Date: March 29, 2013 (final)

Background and Summary Description: Initial approval of NME to improve glycemic control in adults with type 2 diabetes mellitus.

Review

Final labeling including Med Guide and immediate carton and container labels approved via action letter signed by Curt Rosebraugh, M.D., Director ODE-II, on March 29, 2013.

Recommendations

AP letter with appropriate labeling attached and sent to sponsor.

Jena Weber, RHPM	March 29, 2013
Regulatory Project Manager	Date
Chief, Project Management Staff	Date

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

JULIE C MARCHICK
03/29/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204042
Product Name: Invokana (canagliflozin)

PMR/PMC Description: A clinical pharmacology study to evaluate the pharmacokinetics, pharmacodynamics, and safety of canagliflozin in pediatric subjects ages 10 to <18 years with type 2 diabetes on metformin monotherapy. (b) (4)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	10/31/2013
	Study/Trial Completion:	12/30/2014
	Final Report Submission:	06/30/2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   Canagliflozin is ready for approval for use in adults; however, pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This is a deferred pediatric study under PREA to assess the PK, PD and safety of canagliflozin in pediatric patients age 10 to <18 years with T2DM.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacology study in pediatric subjects 10 to <18 years of age with type 2 diabetes on metformin monotherapy to evaluate the pharmacokinetics, pharmacodynamics, and safety of canagliflozin. (b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation)
  Subpopulation: Pediatric subjects ages 10 to <18 years with T2DM

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204042
Product Name:	Invokana (canagliflozin)
PMR/PMC Description:	A 26-week randomized, double-blind, placebo-controlled study, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric subjects ages 10 to <18 years with type 2 diabetes mellitus, as add-on to metformin and as monotherapy (b) (4)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	12/31/2015
	Study/Trial Completion:	06/30/2020
	Final Report Submission:	12/31/2020
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   Canagliflozin is ready for approval for use in adults; however, pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Deferred pediatric study required under PREA to assess the efficacy and safety of canagliflozin compared with placebo when added on to metformin and as monotherapy for the treatment of T2DM in pediatric subjects ages 10 to <18 years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, (b) (4) [redacted] of canagliflozin for the treatment of pediatric subjects ages 10 and <18 years of age with T2DM, as add-on to metformin and as monotherapy, followed by a 26-week double-blind, placebo- or active-controlled extension (b) (4) [redacted]

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation)
  Subpopulation: Pediatric subjects ages 10 to <18 years with T2DM

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204042
Product Name: Invokana (canagliflozin)

PMR/PMC Description: An assessment and analysis of all foreign and domestic spontaneous reports [redacted] (b) (4) of malignancy (pheochromocytomas, Leydig cell tumors, and renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy in patients treated with canagliflozin. [redacted] (b) (4) (b) (4)

The enhanced pharmacovigilance should continue for 10 years from the date of approval for malignancies and 5 years for all other events.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	12/31/2013
	Interim Report Submissions:	05/31/2014
		05/31/2015
		05/31/2016
		05/31/2017
		05/31/2018
		05/31/2019
		05/31/2020
		05/31/2021
		05/31/2022
	Study/Trial Completion:	03/31/2023
	Final Report Submission:	11/30/2023
	Other: _____	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected

☒ Theoretical concern
☐ Other

There is a nonclinical signal for pheochromocytoma, Leydig cell tumors, and renal tubule carcinoma. Given the rarity of these malignancies, enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of this drug.

A case of fatal hemorrhagic pancreatitis occurred with canagliflozin, and there was a slight imbalance in the incidence of serious and overall pancreatitis not favoring canagliflozin. Enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of canagliflozin.

A case of angioedema of the lips occurred with canagliflozin, and an imbalance in skin and hypersensitivity reactions not favoring canagliflozin was noted in the clinical development program. In addition, canagliflozin absorbs light in the UV range that is a concern for photoirritation, and there was an imbalance in the overall incidence and discontinuations due to photosensitivity skin adverse events not favoring canagliflozin. Enhanced pharmacovigilance is required to generate additional data to better assess this serious risk once the product is widely marketed to the general population.

An imbalance in hepatic transaminase elevations (i.e., ALT and AST elevations of 5 and 10x upper limit of normal) was observed with canagliflozin, although no Hy's law case has been identified. Enhanced pharmacovigilance is required to assess the potential for hepatotoxicity once the product has been used in a larger patient population.

Canagliflozin causes renal pelvis and renal tubule dilatation as well as a decrease in the rate of body growth in juvenile rats. Post-natal week 3 to 6 was identified as the time window of susceptibility for the toxic renal effect. This window covers the period of morphological and functional kidney development in rats and would correspond to the second/third trimesters of pregnancy in humans. Therefore, canagliflozin is not recommended for use during the second and third trimester of pregnancy. Enhanced pharmacovigilance is required to generate additional data on canagliflozin exposure during pregnancy, and adverse pregnancy outcomes.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the enhanced pharmacovigilance is to gather additional data on known and potential serious risks related to the long-term use of canagliflozin.

The program will include:

1. Active query of reporters to obtain additional clinical information related to reports of malignancy (pheochromocytoma, Leydig cell tumors, renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy. The sponsor should actively query reporters for the following information:

    a. For reports of pheochromocytoma, Leydig cell tumor, renal cell carcinoma, the sponsor should actively query reporters for laboratory, imaging, and pathology results, duration of canagliflozin exposure, indication for canagliflozin use, canagliflozin dose, patient age, gender, and race (if available), age at first use of canagliflozin, action taken with canagliflozin (e.g., discontinued), concomitant medications including prior exposure to immunosuppressants or antineoplastics, time between initiation of therapy and date of event, comorbid conditions, all supportive studies (pathologic, laboratory, radiologic) – preferably source documents (for phenochromocytoma provide determination of multiple endocrine neoplasia [MEN] Type 1 or 2 or variant), malignancy stage and findings that support the stage (if applicable), other relevant risk factors specific for the malignancy (e.g., smoking, occupational exposures, if applicable), family history of malignancy of at least first degree relatives (if applicable), treatment for the event, event outcome
    b. For reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, the sponsor should actively query reporters for related laboratory values (including triglyceride, lipase, and amylase values), confirmatory imaging and pathology results, duration of canagliflozin exposure, dose of canagliflozin, and other risk factors for pancreatitis.
    c. For reports of severe hypersensitivity reactions, the sponsor should actively query reporters for concomitant medication use, biopsy results, duration of canagliflozin exposure, dose of canagliflozin, and other risk factors for hypersensitivity reactions.
    d. For reports of photosensitivity reactions, the sponsor should actively query reporters for sun exposure, concomitant medication use, duration of canagliflozin exposure, dose of canagliflozin, and other risk factors for photosensitivity reactions.

    e. For reports of serious hepatic abnormalities, the sponsor should actively query reporters for liver-related laboratory (including viral serology), imaging and pathology results, duration of canagliflozin exposure, dose of canagliflozin, and other risk factors for hepatic abnormalities.
    f. For reports of pregnancy, the sponsor should actively query reporters for comorbid conditions, concomitant medication use, other relevant exposures (smoking, alcohol), duration of canagliflozin exposure, dose of canagliflozin, action taken with canagliflozin and the week of gestation at which the action was taken, and the outcome of the pregnancy.

2) Expedited reporting to FDA of all initial and follow-up reports of pheochromocytoma, Leydig cell tumors, renal cell carcinoma, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and adverse pregnancy outcomes.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period. The annual summary and analysis will also include pertinent findings from ongoing or newly analyzed clinical trials and pertinent findings from the published medical literature.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☒ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☒ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Enhanced pharmacovigilance program for reports of pheochromocytoma, Leydig cell tumors, and renal cell carcinoma in patients treated with canagliflozin for a period of 10 years from the date of approval, and for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy for a period of 5 years from the date of approval. The enhanced pharmacovigilance will enable collection of data that will be analyzed to better define these risks and includes the following:

- Active query of reporters to obtain additional clinical information related to reports of pheochromocytoma, Leydig cell tumors, renal cell carcinoma, serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, and pregnancy.
- Expedited reporting to FDA of all initial and follow-up reports of pheochromocytoma, Leydig cell tumors, renal cell carcinoma, serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, and adverse pregnancy outcomes.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Enhanced pharmacovigilance

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204042
Product Name:	Invokana (canagliflozin)
PMR/PMC Description:	Completion and submission of the final report for the 78-week double-blind extension phase of DIA3010, a clinical trial to assess the long-term safety of canagliflozin, including, but not limited to, the effect of the addition of canagliflozin to the addition of placebo on bone mineral density and markers of bone turnover.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	12/31/2013
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

In a 12-week, phase 2, multiple ascending dose study conducted in relatively healthy subjects with type 2 diabetes, use of canagliflozin was associated with a 14 to 28% placebo-adjusted rise in serum markers of bone resorption (collagen type 1 beta-carboxy-telopeptide). The rise was not dose-dependent above a 50 mg per day dose, was observed at Week 3 and persisted to Week 12 inclusive. Changes were also noted in hormones involved in mineral and bone metabolism. Serum parathyroid hormone levels increased from baseline and both 25-OH vitamin D and 1,25-OH vitamin D decreased at high doses.

DIA3010 is a dedicated trial in adults 55 years of age or older with osteopenia (female participants must be at least three years post-menopause). A key objective of this trial is to assess bone turnover markers and bone mineral density using various methodologies over time.

The changes from baseline to Week 26 and 52 in bone turnover markers and in hormones involved in bone metabolism observed in DIA3010 was available at the time of NDA review and showed that canagliflozin causes a statistically significant, dose-dependent, increase in the serum bone resorption marker beta-CTX relative to placebo and variable changes to serum markers of bone formation. These changes have been interpreted as showing the potential to result in changes to bone mineral density. The study also shows that canagliflozin results in a dose-dependent decline in serum estradiol and a slight non-significant elevation in serum PTH.

The significant changes in bone turnover did not have a clinically significant repercussion on placebo adjusted bone mineral density as measured by DXA at Week 52. The sponsor believes the changes are attributable to weight loss and provided examples from the literature to support this assertion.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical trial is to determine whether the changes in bone resorption markers and hormones observed in patients treated with canagliflozin have a clinically significant impact on bone mineral density.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☒ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Completion and submission of the final report for the 78-week double-blind extension phase of DIA3010, a clinical trial to assess the long-term safety of canagliflozin, including, but not limited to, the effect of the addition of canagliflozin to the addition of placebo on bone mineral density and markers of bone turnover.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204042
Product Name: Invokana (canagliflozin)

PMR/PMC Description: A [redacted] (b) (4) randomized, double-blind, placebo-controlled [redacted] (b) (4) [redacted] (b) (4) evaluating the effect of Invokana (canagliflozin) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus [redacted] (b) (4) The primary objective [redacted] (b) (4) should be to demonstrate that the upper bound of the 2-sided 95% confidence interval [redacted] (b) (4) the estimated risk ratio comparing the incidence of MACE (cardiovascular death, non-fatal MI, and non-fatal stroke) observed with canagliflozin to that observed in the placebo group is less than 1.3. [redacted] (b) (4)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	09/30/2013
	Study/Trial Completion:	06/30/2017
	Final Report Submission:	9/30/2017
	Other: _____	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

An estimate of cardiovascular risk derived from a meta-analysis of cardiovascular data across the canagliflozin Phase 2 and 3 programs has provided sufficient evidence that canagliflozin does not unacceptably increase cardiovascular risk to support marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

To support approvability and continued marketing, sponsors of unapproved drugs and biologics developed for the treatment of type 2 diabetes mellitus should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the 2008 Guidance to Industry, "Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes". (b) (4) [redacted] intended to demonstrate that canagliflozin therapy does not result in an unacceptable increase in risk for MACE, i.e., non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

The applicant has already provided sufficient evidence that canagliflozin does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded an unacceptable level of cardiovascular risk. Therefore, consistent with the above guidance, the primary objective (b) (4) [redacted] is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with canagliflozin to that observed with placebo is less than 1.3.

(b) (4) [redacted]

(b) (4) [redacted]

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☒ Assess signals of serious risk related to the use of the drug?
  ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4) randomized, double-blind, placebo-controlled (b) (4) (b) (4) to be conducted in patients with type 2 diabetes at high risk for cardiovascular disease. The primary endpoint will be the time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

(b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial

☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

AMY G EGAN
03/28/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 28, 2012
To:	Mary Parks, M.D., Director **Division of Metabolism and Endocrinology Drug Products (DMEP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Supervisor, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
	Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG)
Drug Name:	INVOKANA (canagliflozin)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 204042
Applicant:	Janssen Research & Development, LLC

1 INTRODUCTION

On May 31, 2012, Janssen Research & Development, LLC, on behalf of Janseen Pharmaceuticals, Inc., submitted a New Drug Application (NDA 204042) for canagliflozin 100mg and 300mg oral tablets to be marketed as a prescription product for the treatment of type 2 diabetes mellitus. Additionally the Applicant submitted, for evaluation by the Agency, a request for Proprietary Name Review for Invocana. Subsequently, the Applicant withdrew Invocana and submitted a request for Proprietary Name Review for Invokana on July 27, 2012. On October 2, 2012, the proprietary name Invokana was approved by the Agency. On March 24, 2013, the Applicant submitted a NDA Amendment for revised carton and container labels in response to the Agency's requirement of a medication guide for canagliflozin.

On February 6, 2012, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed patient labeling for Invokana (canagliflozin) tablets. This review is written in response to a request by Division of Metabolism and Endocrinology Products (DMEP) to review the Applicant's proposed medication guide for Invokana (canagliflozin) tablets.

2 MATERIAL REVIEWED

- Draft Invokana (canagliflozin) Medication Guide (MG) received on March 24, 2013, and received by DMPP on March 26, 2013.

- Draft Invokana (canagliflozin) Prescribing Information (PI) received on May 31, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on March 26, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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

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/s/

TWANDA D SCALES
03/28/2013

MELISSA I HULETT
03/28/2013

LASHAWN M GRIFFITHS
03/28/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	INVOKANA (canagliflozin) tablets, for oral use
Applicant	Janssen Research and Development LLC
Application/Supplement Number	NDA 204042
Type of Application	NME Submission
Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Established Pharmacologic Class[1]	Sodium-glucose co-transporter 2 (SGLT2) inhibitor
Office/Division	ODE II/DMEP
Division Project Manager	Jena Weber
Date FDA Received Application	May 31, 2012
Goal Date	March 29, 2013
Date PI Received by SEALD	March 26, 2013
SEALD Review Date	March 27, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information
[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

NO 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Top margin is 1 inch, instead of 1/2 inch.*

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *HL is > 1/2 page. DMEP will not grant a waiver. Suggestions given to reduce HL length.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment: *There must be white space between the HL limitation statement and the product title.*

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES

Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.
    Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment: *Must read "Revised: March 2013," not "Issued: MM/YYYY."*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS**".

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

Selected Requirements of Prescribing Information

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *Do not bold this statement.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Subsection 13.2 is designated by regulation "Animal Toxicology and/or Pharmacology," not "Reproduction and Development." Revise subsection numbering or heading accordingly in the FPI and TOC.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

JEANNE M DELASKO
03/27/2013

LAURIE B BURKE
03/27/2013

Sukhdev,

As discussed with you, myself and Dr. Egan:

Postmarketing Requirements for Invokana (canagliflozin):

1. A clinical pharmacology study in pediatric patients with type 2 diabetes to evaluate the [redacted] (b) (4) pharmacokinetics, pharmacodynamics, and safety of canagliflozin in older children and adolescent subjects 10 to <18 years of age with type 2 diabetes on metformin monotherapy. [redacted] (b) (4)

   Submit dates for Final Protocol Submission*, Study Completion, and Final Report Submission.

   Allow sufficient time for protocol review, comment, and agreement by FDA (~6 months).

2. A 26-week, randomized double-blind, placebo-controlled trial, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus, as add-on to metformi [redacted] (b) (4)

   Submit dates for Final Protocol Submission*, Study Completion, and Final Report Submission.

   Allow sufficient time for protocol review, comment, and agreement by FDA (~6 months).

3. An assessment and analysis of all foreign and domestic spontaneous reports of malignancy (pheochromocytoma, Leydig cell tumor, and renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy in patients treated with canagliflozin. The enhanced pharmacovigilance should continue for 10 years from the date of approval for malignancies and 5 years for all other events.

The program will include:

a. Active query of reporters to obtain additional clinical information related to reports of malignancy (pheochromocytoma, Leydig cell tumor, renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy. The sponsor should actively query reporters for the following information:

    i. For reports of pheochromocytoma, Leydig cell tumor, renal cell carcinoma, the sponsor should actively query reporters for laboratory, imaging, and pathology results, duration of canagliflozin exposure, indication for canagliflozin use, canagliflozin dose, patient age, gender, and race (if available), age at first use of canagliflozin, action taken with canagliflozin (e.g., discontinued), concomitant medications including prior exposure to immunosuppressants or antineoplastics, time between initiation of therapy and date of event, comorbid conditions, all supportive studies - preferably supplied by the original diagnostic histology report (for phenochromocytoma provide status for multiple endocrine neoplasia [MEN] Type 1 or 2 or variant), malignancy stage and findings that support the stage (if applicable), other relevant risk factors specific for the malignancy (e.g., smoking, occupational exposures, if applicable), family history of malignancy of at least first degree relatives (if applicable), treatment for the event, and event outcome
    ii. For reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, the sponsor should actively query reporters for related laboratory values (including triglyceride, lipase, and amylase values), confirmatory imaging and pathology results, duration of canagliflozin exposure, dose of canagliflozin, and other risk factors for pancreatitis.
    iii. For reports of severe hypersensitivity reactions, the sponsor should actively query reporters for concomitant medication use, biopsy results, duration of canagliflozin exposure, and other risk factors for hypersensitivity reactions.
    iv. For reports of photosensitivity reactions, the sponsor should actively query reporters for sun exposure, concomitant medication use, duration of canagliflozin exposure, dose of canagliflozin, and other risk factors for photosensitivity reactions.
    v. For reports of serious hepatic abnormalities, the sponsor should actively query reporters for liver-related laboratory (including viral serology), imaging and pathology results, duration of canagliflozin exposure, dose of canagliflozin, and other risk factors for hepatic abnormalities.

vi. For reports of pregnancy, the sponsor should actively query reporters for comorbid conditions, concomitant medication use, other relevant exposures (smoking, alcohol), duration of canagliflozin exposure, dose of canagliflozin, action taken with canagliflozin and the week of gestation at which the action was taken, and the outcome of the pregnancy.

b. Expedited reporting to FDA of all initial and follow-up reports of pheochromocytoma, Leydig cell tumor, renal cell carcinoma, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and adverse pregnancy outcomes.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period. The annual summary and analysis will also include pertinent findings from ongoing or newly analyzed clinical trials and pertinent findings from the published medical literature.

Submit dates for Final Protocol Submission*, Annual Assessment and Summary Report Submissions, Study Completion, and Final Report Submission.

Allow sufficient time for protocol review, comment, and agreement by FDA (~6 months).

4. Completion and submission of the final study report for the 78-week double-blind extension phase of study DIA3010, to assess the long-term safety of canagliflozin, including, but not limited to, the effect of the addition of canagliflozin to the addition of placebo on bone mineral density and markers of bone turnover

   Re-submit date for Final Report Submission.

5. A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE – non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE observed with canagliflozin to that observed in the comparator group is less than 1.3. (b) (4)

(b) (4)

Submit dates for Final Protocol Submission*, Trial Completion, and Final Report Submission#.

Allow sufficient time for protocol review, comment, and agreement by FDA (~3 months).

#Please note that your previously submitted date for final report submission of (b) (4) for your cardiovascular outcome trial is not acceptable. The Agency wants to see the final report no later than September 30, 2017. In order to achieve this, you will need to randomize considerably more patients (b) (4) The Agency believes that a total sample size (b) (4) of approximately 10,000 patients is more consistent with cardiovascular outcomes trials being conducted with other anti-diabetic agents, will allow you to achieve the needed number of events in a more timely fashion, and will allow a better assessment of the effect of canagliflozin on cardiovascular outcomes in the early post-randomization period (within 30 days).

*A protocol is not considered final until FDA and the sponsor have reached agreement on it.

Thanks,

Jena

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/s/

JENA M WEBER
03/15/2013
PMR

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 11, 2013

TO: Hyon Kwon, Pharm.D., M.P.H., Senior Clinical Analyst
Jena Weber, Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204042

APPLICANT: Janssen Research & Development, LLC

DRUG: Canagliflozin tablets, 100 mg and 300 mg

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Adults with type 2 diabetes mellitus using canagliflozin as an adjunct to diet and exercise to improve glycemic control

CONSULTATION REQUEST DATE: August 15, 2012
CLINICAL INSPECTION SUMMARY DATE: February 8, 2013
DIVISION ACTION GOAL DATE: March 31, 2013
PDUFA DATE: March 31, 2013

I. BACKGROUND:

Janssen Pharmaceuticals submitted this application to support the use of canagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Canagliflozin is an orally active inhibitor of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is the major transporter responsible for renal glucose reabsorption, and canagliflozin lowers plasma glucose in patients with type 2 diabetes mellitus by reducing renal reabsorption of glucose, thereby enhancing urinary glucose excretion.

The application is based on the results of nine multicenter, randomized, double-blind, placebo-controlled Phase 3 trials.

Six studies were involved with the inspections:

- **28431754DIA3005**, entitled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise" The CANTATA-M Trial (CANagliflozin Treatment and Trial Analysis – Monotherapy)
    - Date study initiated: February 8, 2010
    - Date study completed: August 18, 2011 (last subject out of the 26-week core double-blind period)
    - Study Center(s): A total of 90 sites participated in 17 countries, 33 of which were in North America, 29 of which were in Europe, 10 of which were in Central/South America and 18 of which were in the rest of world.
    - A Phase 3 randomized, double-blind, placebo-controlled, 3-arm parallel-group, global multicenter study composed of a Main Study and a High Glycemic Substudy. The primary objective for the Main Study was to assess the effect of canagliflozin relative to placebo on glycosylated hemoglobin (HbA1c) after 26 weeks of treatment, and to assess the safety and tolerability of canagliflozin.
    - The primary efficacy endpoint was the change in HbA1c from baseline to Week 26.
    - A total of 1,667 subjects were screened. A total of 587 subjects were randomized to placebo, canagliflozin 100 mg and canagliflozin 300 mg in a 1:1:1 manner in the Main Study, and 91 subjects were randomized to canagliflozin 100 mg and canagliflozin 300 mg in a 1:1 manner in the High Glycemic Substudy. The study overenrolled 23% of the target worldwide.

- **28431754DIA3006**, entitled "A Randomized, Double-Blind, Placebo and Active Controlled, 4-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 (Canagliflozin) Compared with Sitagliptin and Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control

on Metformin Monotherapy" The CANTATA-D Trial (CANagliflozin Treatment and Trial Analysis - DPP-4 inhibitor Comparator Trial)

- Date study initiated: April 7, 2010
- Date study completed: October 27, 2011 Core (Week 26 – Period I)
- Study Center(s): A total of 169 study centers in 22 countries, including 55 centers in North America, 51 centers in Europe, 23 centers in Central/South America, and 40 centers in the rest of world.
- A Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group, 4-arm, multicenter study to assess the effect of canagliflozin relative to placebo on hemoglobin A1c (HbA1c) after 26 weeks of treatment and to assess the safety and tolerability of canagliflozin.
- The total duration of the study, including the optional prescreening visit, the 52-week double-blind treatment phase, and the 4-week follow-up period was approximately 59 (for subjects on a protocol-specified dose of metformin at study entry) to 71 weeks (for subjects not on a protocol-specified dose of metformin IR at study entry).
- The primary efficacy endpoint was the change in HbA1c from baseline to Week 26.
- A total of 2,883 subjects were screened and a total of 1,284 subjects were randomly assigned to study treatment in a 2:2:2:1 ratio.

- **28431754DIA3008**, entitled "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus" The CANVAS Trial (CANagliflozin cardioVascular Assessment Study) (Insulin Substudy)
  - Date study initiated: November 17, 2009
  - Date study completed: Study is ongoing; data cutoff for report was September 15, 2011
  - Study Center(s): 369 centers in 24 countries, including 89 centers in North America, 123 centers in Europe, 18 centers in Central/South America, and 139 centers in the rest of the world. The substudy involved a total of 330 centers in 23 countries (81 centers in North America, 16 centers in Central/South America, 112 centers in Europe, and 121 centers in the rest of the world).
  - A Phase 3, randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study designed to evaluate the safety, tolerability, and cardiovascular (CV) risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with type 2 diabetes mellitus, on a wide-range of current antihyperglycemic agents (AHAs), who have either a history or high risk of CV disease. At screening, subjects could be either (1) not on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent for treatment of type 2 diabetes mellitus. The study duration is based upon the occurrence of sufficient events to evaluate the study hypothesis and objectives.
  - The primary measure of efficacy is the hazard ratio (HR) of the composite endpoint of MACE (CV death, nonfatal myocardial infarction (MI), and nonfatal stroke).
  - A total of 7,691 subjects were screened, and a total of 4,330 subjects were randomized, with 1,442, 1,445, and 1,443 subjects assigned to placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

- A total of 2,074 randomized subjects comprised Population 1 (≥ 20 IU) of the insulin substudy. A total of 1,718 randomized subjects comprised Population 2 (≥ 30 IU; includes 83% of the subjects in Population 1) of the insulin substudy. A total of 432 randomized subjects were taking insulin ≥ 30 units/day and metformin ≥ 2000 mg/day at study entry (Population 3 [≥ 30 IU + Met]) of the insulin substudy.
- The total duration of this substudy was 18 weeks.

- **28431754DIA3009**, entitled "A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 100 mg and JNJ-28431754 300 mg Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy" The CANTATA-SU Trial (CANagliflozin Treatment And Trial Analysis Sulfonylurea)
  - Date study initiated: August 28, 2009
  - Date study completed: December 21, 2011 (last subject out of the 52-week core double-blind period)
  - Study Center(s): 157 study centers in 19 countries, including 54 centers in North America, 39 centers in Europe, 9 centers in Central/South America, and 55 centers in the rest of world.
  - A Phase 3, randomized, double-blind, 3-arm, parallel-group, active-controlled, multicenter study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with glimepiride in subjects with type 2 diabetes mellitus with inadequate glycemic control on a maximally effective dose of metformin.
  - The primary efficacy endpoint is the change in HbA1c from baseline through Week 52.
  - A total of 3,316 subjects were screened and a total of 1,452 subjects were randomized to glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner.

- **28431754DIA3010**, entitled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy"
  - Date study initiated: April 12, 2010
  - Date study completed: November 18, 2011 Core (Week 26)
  - Study Center(s): A total of 90 study centers in 17 countries participated, including 46 centers in North America, 23 centers in Europe, 5 centers in Central/South America, and 16 centers in the rest of the world. Body composition substudy: 38 study centers in 10 countries.
  - A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicenter study of subjects with type 2 diabetes mellitus with inadequate glycemic control randomized to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 randomization ratio. The study consists of a 26-week core treatment period followed by a 78-week extension period.
  - The primary efficacy endpoint is the change in HbA1c from baseline through Week

26.
- A total of 716 subjects were randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner.

- **28431754DIA3015**, entitled "A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy" The CANTATA-D2 Trial (CANagliflozin Treatment and Trial Analysis – DPP-4 Inhibitor Second Comparator Trial)
  - Date study initiated: June 30, 2010
  - Date study completed: March 9, 2012
  - Study Center(s): A total of 140 study centers in 17 countries participated, 70 of which were in North America, 21 of which were in Europe, 10 of which were in Central/South America, and 39 of which were in the rest of world.
  - A Phase 3, randomized, double-blind, active-comparator (sitagliptin) controlled, 2 arm, parallel-group, multicenter study of treatment with once daily canagliflozin 300 mg or sitagliptin 100 mg (1:1 randomization ratio) over 52 weeks in subjects with type 2 diabetes mellitus with inadequate glycemic control on the combination of metformin and a SU, with both agents at maximally or near-maximally effective doses. Unlike other studies in the canagliflozin program, this study did not provide glycemic rescue therapy; subjects meeting prespecified glycemic criteria (as applied in other studies for rescue therapy initiation) were discontinued.
  - The primary efficacy endpoint was the change in HbA1c from baseline through Week 52.
  - A total of 1,672 subjects were screened/prescreened and 756 subjects were randomized into the study.

The inspected foreign sites enrolled subjects in three of the nine pivotal studies comprising this application. The inspected domestic sites enrolled subjects in four of the nine pivotal studies comprising this application.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 204042 in accordance with Compliance Programs 7348.811 and 7348.810. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/Site #	**Protocol # and # of Subjects randomized**	**Inspection Date**	**Final Classification**
Alexandrina Popescu Romania Site #40006	DIA3009 18 subjects	1/7/13-1/9/13	Pending Preliminary classification NAI

Pekka Koskinen Sweden Site #46002	DIA3005 24 subjects DIA3008 17 subjects	1/21/13- 1/24/13	Pending Preliminary classification NAI
Elizabeth Bretton USA Site #1002 Site #1346	DIA3005 20 subjects DIA3015 16 subjects	10/22/12- 10/26/12	Pending Preliminary classification NAI
Matthew Acampora USA Site #1087	DIA3006 14 subjects	10/29/12 - 11/01/12	Pending Preliminary classification NAI
Jakkidi Reddy USA Site #1253	DIA3010 22 subjects	11/13/12- 11/16/12	Pending Preliminary classification NAI
Janssen Pharmaceuticals USA	DIA3005 DIA3006 DIA3008 DIA3009 DIA3010 DIA3015	12/03/12- 12/19/12	Pending Preliminary classification NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending.

General Issues Noted at All Sites:
The Sponsor provided the requested data listings using the same data cut-off time point that was used for NDA 204042: the end of each study's 26- or 52-week core double-blind treatment period with the exception of Study DIA3008. For DIA3008, a cut-off date of September 15, 2011 was pre-specified (except data listings for each subject for the primary efficacy endpoint (HbA1c), list of concomitant medications and list of lab abnormalities, the data provided was up to the 18 week primary endpoint of the DIA3008 sub-studies). All other data listings provided for DIA3008 used the cut-off date of September 15, 2011. Source documents at the sites and the CRFs contain data collected beyond the cut-off date of the listings provided with the NDA because the studies were on-going or near completion at the time of the submission Therefore, there were several instances at all sites where the site's source documents for adverse events and concomitant medications match the electronic case report form (CRF), but that information is not reflected in the Data Line Listings provided from the Sponsor.

There were no country specific amendments in effect for the requested sites.

1. **Alexandrina Popescu**
   5 Sighet Ploiesti
   Romania 100163

   a. **What was inspected:** Records for all 27 subjects were reviewed. In addition, IRB, monitor and sponsor correspondences, drug accountability, adverse events, informed consents, protocol adherence, subject records, financial disclosure, safety reports, signature log, monitor log, source documents and electronic case report forms were reviewed.

   b. **General observations/commentary:** A total of 27 subjects were screened, 18 were randomized, 2 dropped out of the study due to adverse events, and 16 completed. The adverse events were reported in the data listings. There were no serious adverse events reported at this site and no deaths.

      The first subject (900304) was dosed on January 5, 2010 and the last subject (903038) was last dosed on November 4, 2012. The expiration date was changed for some medication boxes by the sponsor because they were close to expiration. No left over/returned drug was found at the site at the time of the inspection. The only issue discussed with management was the accountability of the investigational drug that was destroyed. The study monitor verified the number of pills returned in the dispensation record and wrote the medication box number only and not the number of pills that were sent out to eventually be destroyed.

      The FDA ORA field investigator was unable to verify the primary efficacy endpoint data for all the study subjects as the primary efficacy data (the HgA1c values) were not disclosed to the sites. The site sent blood samples to a central laboratory and did not receive the HgA1c values from the lab unless rescue medication was needed. The data for the baseline HgA1c values was disclosed to the site; however, some reports were over a year after the site sent the samples to the laboratory and the laboratory received them. In February 2011 per request of EU Investigators, the sponsor agreed to provide HgA1c results in standard units (IFCC) in addition to the conventional units (%). Following this update, the investigators received re-prints of HgA1c reports with results added in standard units for all subject participating in the study regardless of their screening date. The site did get the screening HgA1c values in a timely manner.

      The 1572 was not available for this site. This was addressed in a memo from the sponsor. For the canagliflozin clinical studies, investigators from foreign sites are not being filed to the US IND (and, therefore, are not required to sign the 1572). The investigator did submit a report of Financial Disclosure and was qualified by the Health Authorities and the Ethics Committee.

      A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form

FDA 483, Inspectional Observations, was issued.

c. **Assessment of data integrity**: The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Pekka Koskinen
Foreningsgatan 26
Malmo Sweden 211 52

a. **What was inspected:** Records for all randomized subjects were reviewed. In addition IRB, monitor and sponsor correspondences, drug accountability, adverse events, informed consents, protocol adherence, subject records, financial disclosure, safety reports, signature log, monitor log, source documents and electronic case report forms were reviewed.

b. **General observations/commentary**: For Study DIA3005, 24 subjects were randomized, 18 completed, 1 subject was lost to follow-up, 3 were withdrawn due to non-compliance, 1 was withdrawn due to adverse events, and 1 was improperly enrolled. For study DIA3008, 17 subjects were randomized, 13 subjects completed, 1 was withdrawn due to adverse events, and 3 withdrew consent.

HbA1c values are only available for Pre-Screening, Screening and Baseline visits since the site was blinded. Therefore, the FDA ORA field investigator was unable to verify the primary efficacy endpoint data as the primary efficacy data (the HgA1C values) were not disclosed to the sites. The information was available for the subjects that needed rescue medication and the information matched the data listings.

Adverse events and concomitant medications which appear in the source documents are also recorded in the eCRF.

A study deviation was filed for subjects 500231 and 500185 after the study monitor found that the fingerstick glucose was not taken at the site at the baseline visit and that compliance could not be checked from the diary (meaning that the study subjects did not record their fingerstick glucose value in their diary either). These two subjects were enrolled and dosed. The fingerstick glucose value is one of the criteria needed to determine subject eligibility. The subjects were kept in the study and continued to be dosed after this deviation was discovered by the study monitor in November 2010.

Further investigation revealed that both study subjects were kept in the study by the PI based on the previous glucose readings from both subjects (before and after baseline – since the issue was discovered after the subjects were randomized) which were stable. The PI subsequently came up with his own check list before randomizing a subject because the check lists and flow charts that the sponsor provided were felt by the PI to

not be clear and complete. This same issue had been reported at 40 other sites for this study.

The 1572 was not available for this site. This was addressed in a memo from the sponsor. For the canagliflozin clinical studies, investigators from foreign sites are not being filed to the US IND (and, therefore, are not required to sign the 1572).

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Elizabeth Bretton
Albuquerque Clinical Trial (ACT)
601 Encino Place NE, Suite A16
Albuquerque, New Mexico 87102

a. **What was inspected:** The numbers of subject records reviewed during the inspection were 32 for Study DIA3005 and 25 for Study DIA3015. During this inspection, regulatory records, subject files, electronic records, and other study-related documents were reviewed. Source documentation was reconciled with eCRF entries, IRB submissions (both for approval of the study and related documents, as well as informational submissions such as adverse events), were reviewed for timeliness, and correspondence with sponsor/monitor was documented throughout both studies.

b. **General observations/commentary**: For Study DIA3005, the total number of subjects screened at the site was 32, total number enrolled was 20, and total number completing the study was 19. One subject withdrew as he lost his job and home and could not comply with the study schedule or procedures. For Study DIA3015, the total number of subjects screened at the site was 25, the total number enrolled was 16, and the total number completing the study was 7. Five subjects withdrew consent, one had a HgbA1c that was too high, and one was withdrawn due to PI decision. No Serious Adverse Events or subject deaths occurred at this site during either study.

(b) (4) monitored the studies. All subjects signed the informed consent. However, the site utilized a photocopied form to document their Informed Consent process. This form appeared to have been signed once, then photocopied and placed in every subject's files (for study DIA3005). This process was considered inappropriate and was discussed with the PI and staff. The Site

Final Report forms for both studies were submitted to the IRB on February 28, 2012.

Hardcopy records were maintained on site and were readily available for review during this inspection. Records were well organized and legible, although there were some instances where information was written-over on a handwritten record instead of lined-out, initialed, dated, and changed. The eCRFs for Study DIA3015 were provided on a CD-ROM. The eCRFs for Study DIA3005 were not available from the sponsor on CD-ROM but were able to be accessed through the password protected web-based portal for review during the inspection.

This site remains blinded to the subject's status (test, control, or placebo). This site sent blood samples to a central laboratory, (b) (4) for study-related labs such as the HgA1c (a primary efficacy endpoint). The site did not receive the HgA1c values from the lab unless the value met certain criteria which would require treating the subject with additional medications for their safety (e.g. some subjects required metformin "rescue" as their HgA1c was too high). However, in general this site did not receive HgA1c values beyond the screening visits; thus, the screening visit value was compared to the data line listing to determine accuracy, however, the 26-week HgA1c was not available at this site to compare to the data line listing.

Other data compared from this site (via source documentation and eCRF submissions) that was compared to the data line listings included adverse events and concomitant medication. The FDA ORA field investigator found several instances where data did not appear consistent (i.e. data from the eCRF was not consistent with the data line listing). It was determined that the source data contained events that occurred after the data cut-off for reporting the data line listings.

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted. Data from this site are acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. Matthew Acampora
The Center for Nutrition and Preventive Medicine
8035 Providence Rd., Suite 315
Charlotte, North Carolina 28277

a. **What was inspected:** There were 14 subject records reviewed. The current inspection included a review of IRB, monitor and sponsor correspondence, drug accountability, adverse events, informed consents, protocol adherence, subject records, financial disclosure, safety reports, signature log, monitor log, FDA 1572s, curriculum vitas,

laboratory credentials and other supply records, source documents and electronic case report forms.

b. **General observations/commentary**: There were 39 subjects consented at the site and 14 enrolled. There were 8 subjects that completed the study but the data line listing submitted to the FDA has 9 (both the clinical investigator and the sponsor representative at the site confirmed that 8 subjects completed the study). Ten subjects withdrew from the study or were terminated. One was lost to follow-up, 3 had adverse events and 6 withdrew consent.

The source documents were well organized and legible. There were no instances where the data reported by the clinical investigator did not match the data reported to the FDA in the NDA data line listings. All adverse events appeared to have been captured. There was one incidence (Subject 600313) where anxiety was listed but this history was not found in the source documentation.

(b) (4) monitored the study. The study was initially approved on February 26, 2010. The Site Final Report form was submitted to the IRB on April 12, 2012. Four informed consent forms were approved to be used during this study and three were used at this site. All subjects signed informed consent. It was noted that Subject 600016 had his wife print his name on several of the informed consent documents; however, subject did sign his name and initials.

Electronic case report forms (eCRFs) were submitted to the sponsor. Dr. Acampora did not have a CD-ROM containing all eCRF data at the time of this inspection. According to the Sponsor's most recent newsletter, the final Clinical Study Report was expected to be released on 10/31/12 and the CD-ROM containing all eCFR data that was generated at this site was to be mailed to the Clinical Investigator.

The FDA ORA field investigator had access to the screening HgA1c but not the serial values collected throughout the study and was, thus, unable to verify the primary efficacy endpoint data. The site remains blinded to the subject's status. The site sent blood samples to a central laboratory, (b) (4) for study-related labs such as the HgA1c (a primary efficacy endpoint). The site did not receive the HgA1c values from the lab unless rescue medication was needed.

All patients that required rescue medication had results unblinded and these HgA1c results were compared to the data line listing. Two subjects (600241 and 600285) needed rescue medication. (b) (4) (the central lab) released the elevated HgbA1c results in these two cases as per the protocol. The lab value was unmasked, but the study drug was never unblinded.

There was one other subject (600022) that (b) (4) released the elevated HgbA1c value, but Dr. Acampora did not prescribe a rescue medication. The subject had several issues that Dr. Acampora felt contributed to the slightly elevated results and he wanted to try other options (diet, etc.) before issuing a new medication. The subject's

next test interval was normal. It was discussed with Dr. Acampora that this was a protocol deviation.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted. Data from this site are acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. Jakkidi Reddy
Sierra Clinical Research, Inc.
576 N. Sunrise Ave., Suite 230
Roseville, California 95661

a. **What was inspected:** All 22 randomized subject charts were reviewed. Documents reviewed included, but were not limited to, Form FDA 1572s, financial disclosure forms, IRB correspondence, sponsor correspondence, monitor correspondence, informed consent forms, protocol deviations, documentation of adherence to protocol procedures, inclusion/exclusion criteria, adherence to blinding/randomization procedures, source documentation for each subject enrolled, electronic case report forms, safety endpoint data, adverse events, and concomitant medications.

b. **General observations/commentary**: There were 42 subjects screened at the site, 22 were randomized, 11 subjects completed the study, 8 were currently in progress, 2 withdrew, and 1 was an early termination. The first subject was randomized on June 2, 2010. The study was on-going at the time of the inspection and the last subject was randomized into the trial with an expected completion date of February 28, 2012.

The eCRFs were reviewed and compared to the source documents and data line listings. Overall, records reviewed appeared adequate and there were no instances of unblinding of the study. Records were well organized and legible, although there were some instances where accountability logs had a number of cross-outs, incorrect entries, and illegible markings. Drug accountability records were reviewed and were complete.

The FDA ORA field investigator had access to the screening HgA1c but not the serial values collected throughout the study and was, thus, unable to verify the primary efficacy endpoint data. The site remains blinded to the subject's status. The site sent blood samples to a central laboratory, (b) (4), for study-related labs such as the HgA1c (a primary efficacy endpoint). The site did not receive the HgA1c values from the lab unless rescue medication was needed.

(b) (4) monitored the study. Initial IRB approval was March 18, 2010. There were 3 informed consent documents utilized at the site. All received IRB approval. A total of approximately 66 IC forms

were reviewed and all subjects signed all versions of the informed consent form except for one document that was missing a signature. However, all pages were initialed by the subject. It was discovered by staff and the subject signed the IC on the next visit.

All financial disclosure forms were reviewed and appeared adequate.

A few minor discussion items were raised to Dr. Reddy's attention during the close-out meeting. One subject was inadvertently tested twice for HbgA1c. One subject gave his spouse the investigational medication. One subject file had vital signs missing.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted. Data from this site are acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

6. Janssen Pharmaceuticals
920 Route 202 South
P.O. Box 300
Raritan, NJ 08868

a. **What was inspected:** The following areas were given coverage: monitoring, test article accountability, case report forms, regulatory forms (Form 1571, Form 1572 and Financial Disclosure), (serious) adverse events (evaluation and reporting), standard operating procedures, and computer systems (eCRF, Dashboard, disaster preparedness / recovery), adjudication process, and site selection.

The clinical project /program consisted of nine protocols conducted in approximately 1,500 clinical sites over approximately 48 countries around the world.

Records were reviewed for at least 45 subjects from those clinical sites identified. Financial disclosure forms were reviewed for at least 45 clinical investigators. Form FDA 1572s were reviewed for at least 45 clinical investigators whose study was conducted within the USA. Monitoring reports were reviewed for at least six clinical sites. Standard operating procedures reviewed included those relating to adverse events and SUSARs evaluations, investigational product, and monitoring.

During the inspection, the training of the clinical site monitors and clinical investigators were reviewed. Special attention was given to those clinical monitors hired from contract research organizations.

During the inspection, transfers of obligations were reviewed.

Janssen Pharmaceuticals acted as the sponsor for studies (previously named Johnson &

Johnson Pharmaceutical Research & Development). Johnson & Johnson received a Warning Letter on (b) (4) and as a result of the issuance of this Warning Letter, OSI staff conducted an OAI follow-up inspection of Johnson & Johnson in 2010 and looked at select canagliflozin studies when they were ongoing. The follow up inspection identified Protocol 28431754DIA3008 as one of the protocols to be reviewed with respect to the corrective actions implemented by Johnson & Johnson. Deficiencies were noted and the ORA inspector was asked to determine whether these deficiencies had been appropriately addressed and resolved by the sponsor.

b. **General observations/commentary**: Inspection revealed clinical sites were monitored by clinical research associates who were employees of Janssen R&D, employees of contract research organizations and clinical research associates who were employees of the contract research organizations who were dedicated to Janssen R&D for the conduct of these clinical protocols.

During the conduct of the study, the following responsibilities were not conducted by the sponsor, rather by a party, which is summarized below:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

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(b) (4) were not listed on the Form FDA 1571.

The independent data monitoring committee (DMC) convened approximately every six months for the purpose of reviewing the study data. During the inspection, the following documents were reviewed: charter, meeting minutes, financial disclosure form and curriculum vitae. The information self-declared by the committee members, the information provided on the financial disclosure form and on the curriculum vitae by the members of the DMC were not verified by Janssen R&D.

Limited inspection of the manufacturing operation was conducted for the clinical batches released for use during the conduct of these studies. Inspectional coverage was given to the release specification which was limited to visual inspection and dissolution of the over-encapsulated tablets.

No significant observations were noted during the inspection.

The inspectional findings indicate adequate oversight and adherence to good clinical practice regulations. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of three domestic and two foreign clinical sites as well as the sponsor. No site was issued a Form FDA 483; the preliminary classifications are all NAI (No Action Indicated). In general, based on the inspection of the five clinical study sites and the sponsor, the inspectional findings support validity of data as reported by the sponsor under this NDA.

Observations noted above for Drs. Bretton, Acampora, and Reddy, and the sponsor are based on the preliminary review of the Establishment Inspection Reports. Observations noted above for Drs. Popescu and Koskinen are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

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02/11/2013

SUSAN D THOMPSON
02/12/2013

JANICE K POHLMAN
02/12/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	January 30, 2013
Reviewer:	Reasol S. Agustin, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Invokana (Canagliflozin) Tablets, 100 mg and 300 mg
Application Type/Number:	NDA 204042
Applicant/sponsor:	Janssen, LLC
OSE RCM #:	2012-1302

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Invokana (Canagliflozin) Tablets, NDA 204042, for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Applicant submitted the proposed container label, carton and insert labeling for the proposed proprietary name, Invokana on November 15, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 15, 2012 submission.

- Active Ingredient: Canagliflozin
- Indication of Use: Treatment of Type 2 Diabetes Mellitus
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 100 mg and 300 mg
- Dose and Frequency: 100 mg or 300 mg once daily
- How Supplied: 30-count, 90-count, and 500-count bottles; Blister package containing 100 tablets (10 blister cards containing 10 tablets each)
- Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F)
- Container and Closure Systems:
  - 100 mg: [redacted] (b) (4)
  - 300 mg: [redacted] (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted November 15, 2012 (Appendix A)
- Carton Labeling submitted November 15, 2012 (Appendix B)
- Insert Labeling submitted November 15, 2012

3 CONCLUSIONS

DMEPA concludes that the proposed container and unit dose labels as well as carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label; 100 mg and 300 mg strengths (30-count, 90-count, and 500-count bottles)

1. Revise the presentation of the proprietary name to Title Case "Invokana" to improve readability and legibility because as currently presented, all the letters in the proprietary name are all the same size, thus decreasing readability.
2. Remove the graphic that appears above the letter 'V' in the proprietary name, Invokana.
3. Relocate the statement "Each tablet contains 100 mg canagliflozin" on the principal display panel to the side panel.
4. Increase the font size and prominence of the dosage form "Tablets" so that it is presented with the same size and prominence as the established name "(canagliflozin)." If needed, the strength presentation may be moved to the next line, immediately below the dosage form, "Tablets."
5. Ensure that the image of the tablet accurately represents the actual size, shape, color, and imprint of the commercial tablet and is not a schematic or computer-generated shape or image. In addition, this image should be less prominent and located away from important information such as proprietary name, established name and strength. Thus, relocate the tablet image to appear at the bottom of the principal display and side panels.

B. Container Label; 100 mg strength (500–count bottle)

1. The 300 mg strength, 500-count bottle has the statement "Package Not Child-Resistant" but this statement is not placed on the 100 mg strength 500-count bottle. Please add this statement on the 100 mg strength 500-count bottle, so that both labels are consistent.

C. Hospital Unit Dose Label

1. Revise the presentation of the proprietary name to Title Case "Invokana" to improve readability and legibility because as currently presented, all the

letters in the proprietary name are all the same size, thus decreasing readability.

D. Carton Labeling for Hospital Unit Dose

1. Revise the presentation of the proprietary name to Title Case "Invokana" to improve readability and legibility because as currently presented, all the letters in the proprietary name are all the same size, thus decreasing readability.
2. Remove the graphic that appears above the letter 'V' in the proprietary name, Invokana.
3. Relocate the statement "Each tablet contains 100 mg canagliflozin" on the principal display panel to the side panel.
4. Increase the font size and prominence of the dosage form "Tablets" so that it is presented with the same size and prominence as the established name "(canagliflozin)." If needed, the strength presentation may be moved to the next line, immediately below the dosage form,"Tablets."
5. Ensure that the image of the tablet accurately represents the actual size, shape, color, and imprint of the commercial tablet and is not a schematic or computer-generated shape or image. In addition, this image should be less prominent and located away from important information such as proprietary name, established name and strength. Thus, relocate the tablet image to appear at the bottom of the principal display and side panels.
6. Revise the statement [redacted] (b) (4) to read "100 tablets (10 blister cards with 10 tablets per blister card)." Currently, the statement [redacted] (b) (4) and may be confusing to the end user.

E. Insert Labeling

1. The symbols <, ≤, >, ≥ were utilized in the insert labeling to represent "less than," "less than or equal to," "greater than," or "greater than or equal to," respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. As part of a national campaign to decrease the use of dangerous symbols[2], the FDA agreed not to use such error prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, DMEPA recommends that < be replaced with "less than," ≤ be replaced with "less than or equal to," > be replaced with "greater than," and ≥ be replaced with "greater than or equal to."

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

[2] Institute for Safe Medication Practices (ISMP). ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

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

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/s/

REASOL AGUSTIN
01/30/2013

YELENA L MASLOV
01/30/2013

CAROL A HOLQUIST
02/03/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	12 December 2012
To:	Mary Parks, M.D., Division Director Division of Metabolic and Endocrine Products
Reviewer:	Leonard Seeff, MD, Hepatologist Office of Surveillance and Epidemiology
Through:	Allen Brinker, MD, MS, Medical Team Leader Division of Pharmacovigilance 1
Drug Name:	canagliflozin
NDA Number:	204-042
Applicant/sponsor:	Janssen
OSE RCM #:	2012-2473
Issue:	Review of a cases of liver injury in association with canagliflozin

Executive Summary

Although plagued by the common problem of missing data or a competing cause for liver injury not sought, thus creating difficulty in absolutely ruling out drug-induced liver disease (dili) or in establishing an alternative diagnosis, there is little compelling evidence in review of these cases to implicate canagliflozin as a drug clearly capable of causing dili if it occurred. There are a few instances in which this diagnosis cannot be absolutely excluded because all possible alternative diagnoses have not been excluded or data are lacking, but most of these are cases of relatively mild liver disease. The diagnoses in some of them may be resolved if the sponsor is able to produce additional information.

In sum, based on this group of cases selected for review, no signal for hepatotoxicity is appreciated for canagliflozin at this time.

Background

This review is based on a consult request for the Division of Metabolic and Endocrine Products (DMEP) dated 18 October 2012 to review selected cases of potential drug-induced liver injury (dili) in association with canagliflozin (NDA 20-4042). Canagliflozin is currently under review by the Agency as an oral agent for the treatment of DM2.

As noted in the consult request, DMEP noted a slight imbalance (against cangliflozin) in the incidence of subjects with ALT > 5X ULN and >10X ULN and in incidence of subjects meeting biochemical Hy's law in registrational trials. DMEP requests a review of selected cases by OSE's hepatology consultants including comment on the significance of the overall imbalance based on the findings from your review.

This review is organized in 3 sections (A, B, and C) based on the organization of the consult request.

Review of Cases

Part A: Request for review of two cases regarded as unlikely DILI by sponsor's Hepatic Events Assessment Committee (HEAC)

ID (b) (4)

This was a 61 year-old man with a history of type 2 diabetes, diabetic neuropathy, hypertension, osteoarthritis and arthroplasty of the right hip. He had apparently been treated with metformin for his diabetes, but the actual start date of this drug was not reported. On a background of normal baseline liver chemistries (ALT, AST, ALP, Bilirubin, GGT), he was started on treatment with canagliflozin on March 31, 2010. Over the course of the following year and a half, liver panel testing was performed at approximately 3 month intervals and remained completely normal until June 31, 2011 (approximately 15 months after starting treatment with canagliflozin). The next series of tests were performed on September 8, 2011 with results that are disputed. Apparently,

another patient was seen at the same site and same day 10 minutes after the present subject, and had blood drawn that was found to have markedly elevated liver tests (the actual values not reported). The sponsor believes that the test results were switched between the two subjects and that the present subject in fact had quite normal chemistries. The information presented is, however, somewhat confusing. Blood drawn 3 weeks later from the present patient (September 27, 2011, now about 18 months after starting the drug) revealed obviously abnormal liver chemistries (ALT 905 IU/L; AST 478 IU/L; alp 123 IU/L. Bilirubin 2.0 mg/dl; and GGT 697 IU/L). That this was not a transient finding is evident by the fact that in three subsequent blood draws, similar abnormalities were found although slowly improving. The last set of values shown, on October 17, 2011, 20 days after the first reported abnormalities, displayed values that were still abnormal (ALT 195 IU/L; AST 60 IU/L; Alp 98 IU/l, Bilirubin, 1.1 mg/dL, and GGT 370 IU/L).

The precise cause of the abnormal liver chemistries is unclear. It is almost certainly not a consequence of treatment with canagliflozin because of the latency of 18 months from start of drug even though improvement occurred with withdrawal; however, improvement was apparent even before drug withdrawal. Serologic tests for hepatitis A and B excluded these two conditions. The patient is reported to be positive for anti-HCV but the test for HCV PCR is pending as are the tests for ANA and EBV. The patient was started on treatment with pioglitazone September 8, 2011 that was terminated on October 2, 2011 by which time, the enzyme values had already begun to decline.

Comment: Canagliflozin hepatotoxicity is almost certainly ruled out as a cause because of the 18 month latency and the fact that the enzyme levels began to decline even before withdrawal of the drug. The subject did develop late in follow-up what appears to be acute hepatocellular liver injury with hyperbilirubinemia but without jaundice. The cause for the liver injury is unclear. The timing of the start and stop dates of pioglitazone relative to the identified liver injury makes liver injury from this drug highly unlikely. Not ruled out are infection from hepatitis C and E. A positive test for either would provide useful information to help resolve the diagnosis.

ID (b) (4)

This request represents a case that has been reviewed several times in the past by this reviewer and Dr. John Senior during which times no definitive diagnosis for the observed liver dysfunction could be reached for this case. The view on each of these occasions was that the available data were insufficient to achieve a diagnosis of what appeared to be a cholestatic form of liver disease that developed about 8 months after starting treatment with canagliflozin. The last set of data reported at the time was from October 19, 2011. A review was submitted in November 2012.[1]

The sponsor has now submitted additional work-up data, providing information to as recently as mid-July, 2012.

Briefly, this was a man in his late 60's who had participated in a double-blind, placebo-controlled trial and who was admitted to hospital with abdominal pains, chills, nausea and vomiting approximately 8 months after starting the trial. He had been in the treatment arm that received canagliflozin. The patient had also been on multiple other drugs for his diabetes, hypertension, coronary artery disease, and gastro-esophageal reflux. His liver chemistries showed moderate increases in his aminotransferases and alkaline phosphatase as well as a significant increase in his serum bilirubin value. In general, the pattern of injury suggested cholestatic liver disease and biliary tree disease was suspected but initial evaluation was unable to prove this diagnosis. An ultrasound scan and magnetic resonance cholangiopancreatography of the upper abdomen was unrevealing. Noteworthy is that despite discontinuing canagliflozin, the abnormal chemistries persisted. Despite the fact that he had been evaluated at two different hospitals, the diagnosis remained unclear. Indeed, a liver biopsy that was considered worth performing was cancelled because the liver chemistries showed improvement, yet the serum enzymes and serum bilirubin still remained elevated, although at a lower level. He continued to complain of severe pruritus. Drug-induced liver injury remained suspect

[1] John Senior and Leonard Seeff to Mary Parks. Possible hepatic adverse effects of canagliflozin. 28 November 2012.

but uncertainty was expressed regarding whether it was due to canagliflozin or other drugs (simvastatin, pioglitazone) although the injury pattern was atypical for these drugs.

Additional follow-up data have since revealed that he has continued to have abnormal liver chemistries with moderate increases in his aminotransferase levels, some higher increase in ALP levels and persisting modest hyperbilirubinemia. A liver biopsy was performed on November 11, 2011 and was reported to show prominent proliferative duct reaction, cholestasis and portal fibrosis, interpreted at first as displaying hepatic duct stenosis and later as a "biliary tract process." In January, 2012, he had an MRI with contrast of the abdomen that showed an "irregular intrahepatic biliary tree with moderate peripheral intrahepatic biliary dilatation and normal appearing extrahepatic bile ducts." In February, 2012, an ERCP was performed that showed several segments of mild to moderate narrowing of the intrahepatic bile ducts now raising the specter of sclerosing cholangitis. Putting this together, a hepatology consultant raised the possibility of primary biliary cirrhosis. However, as best as can be determined from the report of the liver biopsy, PBC was not raised as a possible diagnosis. Moreover, there is no report of testing for anti-mitochondrial antibody. Also of note is that the hepatologist involved felt that the manifestations in this patient were not typical for sclerosing cholangitis and that the presentation was more likely that of drug induced liver injury. In June, 2012, the patient was hospitalized because of increasing jaundice, weakness and chills attributed then to sclerosing cholangitis. He was treated with antibiotics. At this point, the possibility of performing liver transplantation was raised.

Comment: This is an extraordinary odyssey for this patient who has now had prolonged low grade jaundice that seemed to begin about 8 months after starting treatment with canagliflozin. He was taking many other drugs but there is still no information regarding start and stop dates for these drugs. It is clear that the liver disease has shown a cholestatic pattern with bouts of what appeared to have been cholangitis. It is clear also that the disease process has been advancing with the most recent consideration for performing a liver transplantation although I don't see definitive evidence of end-stage liver disease. I believe that the features of this illness are consistent with sclerosing

cholangitis. This, of course, raises the question of whether canagliflozin might have been the precipitating event. Three sets of liver chemistries following the beginning of treatment with canagliflozin were normal, which might suggest that the drug could have played a role. However, it is not atypical for sclerosing cholangitis to have sporadic liver dysfunction early in its course so that, in my view, these normal values do not exclude a diagnosis of "idiopathic" sclerosing cholangitis, which represents my current diagnosis. I cannot entirely exclude the possibility that canagliflozin did play a role in inducing this liver disease, but I would grade it as an extremely low possibility.

Part B: Request to review two phase 3 development cases with jaundice

ID 2062301

Minimal information is provided for this case that involved a 64 year-old man who developed deep jaundice, moderately elevated aminotransferase levels and markedly elevated alkaline phosphatase levels. Little information is provided other than a final diagnosis of biliary tree cancer. The biochemical values are consistent with this diagnosis and there are no data provided to dispute this.

ID T060404

Once again, the information provided here is minimal, as evidenced in part by the fact that only one set of liver chemistries is shown. This describes a 68 year old man with DM2 who, 24 weeks after starting treatment with canagliflozin, developed abnormal liver-related chemistries (ALT 296 U/L, AST 106 U/L, ALP of 481 U/L, and a total bilirubin value of 0.7 mg/dL. No other values are shown, but an abdominal US showed intrahepatic duct dilatation, a CT scan showed pancreatic duct narrowing, retroperitoneal fibrosis and interstitial nephritis together with elevated IgG4 levels. These findings are apparently reflective of "autoimmune pancreatitis." It would, however, have been helpful to have additional laboratory values to determine which direction they were moving in, specifically to learn whether the abnormal values persisted or subsided, and whether jaundice developed. Thus, the sponsor could provide additional information and whether

any other potential diagnoses were sought. However, the available information does point to autoimmune pancreatitis.

Part C: Request to review cases of "severe hepatic enzyme elevation or liver failure" to determine agreement with the applicant's assessment of causality

There are 18 cases in this category, but many of them were either poorly evaluated for causality or provided incomplete data.

ID 500611

This 50 year old female developed a transient mild increase in ALT, AST and ALP on day 15 of treatment with immediate return to normal but followed by a more marked increase in serum enzymes with fluctuating levels thereafter until day 393, the last value shown. Bilirubin apparently remained normal throughout. The drug was discontinued just before a marked increase in the values. Tests for hepatitis A, B, and C were negative. Markers for autoimmune hepatitis were not reported. The patient did have a background of cholelithisis that conceivably could have accounted for the abnormalities. However, there is uncertainty about what the cause was for these abnormalities that seem to have persisted for 8-9 months without resolution. This reviewer does not suspect that the drug was responsible although uncertainty remains. It would be interesting to know what the sponsor's experts think about this case.

ID 150867

This 63 year old man had abnormal liver-related chemistries from the outset, although there was a sudden marked increase in the ALT, AST and ALP on day 85 lasting through day 149 without an increase in the bilirubin level. A hepatitis panel revealed that the patient had chronic hepatitis C. Accordingly, this is not an instance of drug induced liver injury.

ID 601010

This 28 year old man had evidence of necroinflammatory liver disease beginning on day 1 of treatment, so clearly this is not a case of dili. This appears to be a case of chronic hepatitis C based on the finding of anti-HCV but no test for HCV RNA is provided. It is also interesting that there is a single set of values on day 72 that are quite normal. Does this signify recovery from hepatitis C, which would be unusual?

ID 601977

This 68 year old man had abnormal liver chemistries from before and at the time of starting treatment ruling out dili as a cause for the abnormalities. Data reported are skimpy but the values, although fluctuating into the normal range, were still abnormal when the patient was last seen. Thus, this appears to be chronic necro-inflammatory liver disease but the cause is not apparent. Hepatitis serology was not reported, information that should be made available by the sponsor.

ID 602444

This was a 40 year old female who developed a single set of abnormal aminotransferase levels at week 85 of treatment that returned to normal immediately thereafter. Since the drug continued to be taken and the liver chemistries nevertheless normalized, this is not a case of dili. The reason for the single abnormality is not clear.

ID 602764

This 64 year old female with normal liver chemistries baseline was found to have moderate to marked increases in her liver chemistries beginning on day 85 (although no blood test results are reported between day 46 and day 85). The serum bilirubin value was normal. The drug was discontinued on day 87. The abnormal values gradually decreased but were still slightly abnormal on day 95, the last value shown. Hepatitis serology A, B, and C were negative as were ANA and SMA. Thus this is an acute but mild hepatitis without an obvious etiology. What needs to be determined is whether the patient developed acute hepatitis E, and the sponsor should be queried on this point. Until this is done and the results reviewed, a diagnosis of mild dili cannot be ruled out. Indeed, this

could be a possible to probable dili, a diagnosis that would be reversed if testing supported a diagnosis of acute hepatitis E virus infection.

ID 602830

This 35 year old woman with normal baseline liver chemistries was found to have mild increases in her ALT levels beginning on day 85 increasing by day 179, although no values are shown for the period between day 121 and day 179. Thereafter, the values remained abnormal up to the time of the last set of values tested, on day 310. The drug was withdrawn on day 277. This appears to be an instance of chronic necro-inflammatory disease with an undetermined etiology. This could conceivably be a case of acute progressing to chronic hepatitis C, but no serology for any of the hepatitis viruses was reported. Until then, dili cannot be ruled out as a cause for the liver injury that could be graded as at least possible and perhaps even probable.

ID (b) (4)

This 66 year old man has cryptogenic cirrhosis without evidence of dili.

ID (b) (4)

This 64 year old man developed a lymphoproliferative disorder and apparent cholecystitis with septicemia that was apparently responsible for his death. He did not develop dili.

ID (b) (4)

This 61 year old man developed an acute hepatitis on day 282 of treatment that was diagnosed as acute hepatitis E. He was also found to have a hepatic cyst. There is no evidence of dili.

ID (b) (4)

This was a very well worked up case involving a 66 year old man who developed abnormal serum enzymes and quite deep jaundice on day 237 of treatment. The enzymes have remained normal although fluctuating until day 412 at a slightly lower level. Treatment was discontinued on day 239. The bilirubin level was still abnormal on day

412 although also reduced. All hepatitis serology, including for hepatitis E as well as for autoimmune hepatitis, were negative, as was the test for CMV. However, one of the tests for EBV was positive. The latency in this case was prolonged beyond that consistent with dili, but still the diagnosis in this case is unclear to me. There was a slight suggestion that the patient had cholecystitis. Dili cannot be completely ruled out as a diagnosis. Further information from the sponsor would be desirable.

ID (b) (4)

This was a 68 year old man whose liver chemistries remained normal until day 131 of treatment. The next test reported was on day 275, a huge gap from the prior test that displayed an ALT value of 302 and an AST of 95. That was the last value shown. The patient withdrew consent for further treatment on day 274. No information can be expected. A diagnosis of dili is unlikely given the long latency.

ID (b) (4)

Minimal information supplied regarding this 68 year old woman who developed modestly elevated ALT, AST and ALP values on day 260 of treatment that fell almost to normal one week later. This represents latency generally beyond that of dili, but the cause is unclear. One suggestion is that EBV infection might have played a role. It would be useful to obtain further follow-up information on this case.

ID (b) (4)

This is an absolutely inexplicable case. This 63 year old woman had completely normal liver chemistries except for a dramatic increase of the ALT to 2075 U/L, the AST to 3969 U/L, with normal ALP and bilirubin values on day 41 of treatment. The values immediately thereafter are normal and the patient had no symptoms. The sponsor believes that there was a mix up in samples or there was something amiss with the testing. I concur and believe this is not dili.

ID (b) (4)

Once again, the information supplied here is somewhat skimpy. This was a 75 year old man started on treatment with canagliflozin who had normal liver chemistries; unfortunately, there were only a small number of test results reported. On day 285 of treatment, he developed vomiting and diarrhea, and was found to have moderate elevations of his aminotransferase levels. His bilrubin and ALP values remained normal. The drug was discontinued 3 days later. He was found to have diabetic ketoacidosis for which he was successfully treated. The serum enzyme levels normalized fairly rapidly and were back to normal by day 301. Serologic tests for hepatitis A, B, and C were non-reactive and US evaluation suggested the presence of a small gallstone or polyp. The precise cause for the transient but relatively mild increases in the serum enzymes remains uncertain. Were it not for the fact that this would represent an unusually prolonged latency between start of treatment and onset of liver injury, this could be considered a possible instance of dili.

ID (b) (4)

This 63 year old woman had mildly abnormal aminotransferase levels at the beginning of treatment that returned to normal on day 85 and then increased considerably when next tested on day 183 (why no tests in the interim?). The few tests obtained thereafter showed improvement but still abnormal values up to the last test reported. The drug was withdrawn on day 223 over a month after the increased values were found and after the values had begun to decline, suggesting that the drug was not responsible for the injury. This patient appears to have chronic liver disease from the outset but surprisingly, the only hepatitis serology reported was that of hepatitis A. Accordingly, chronic hepatitis B and C, and of course autoimmune hepatitis, are not ruled out as potential etiologies. A major problem in this case is that there are relatively few results of liver-related tests reported and that they are far-spaced. There is uncertainty in whether or not this is dili but the possibility is quite low. More information from the sponsor would be helpful in determining the etiology of the liver dysfunction.

ID (b) (4)

This 56 year old man had fluctuating abnormal aminotransferase levels from the beginning of treatment through to the last value shown, on day 515. During this period, the study drug was interrupted for relatively short periods and finally withdrawn on day 473. Because values were abnormal from the outset, this is not a case of dili but the actual cause for the abnormalities remains unclear. His hepatitis serology (A, B, C) and autoimmune serology were non-reactive, but there is a hint of EBV infection. The sponsor believes that the abnormalities were due to steatosis but the criteria for this diagnosis are quite spotty.

ID (b) (4)

As is the case for many of these reports, the data presented are meager. This was a 59 year old woman with normal baseline liver chemistries who was found to have raised values for ALT, AST and bilirubin on day 98 of treatment; however, no values are reported between the baseline testing and day 98. The next tests were reported from day 104 which showed a decline in the abnormal chemistries. Shortly thereafter, the drug was withdrawn (values has already begun to decline prior to this) and the last value shown, on day 116, was still abnormal although less so. Testing for hepatitis B and C showed negative results, but tests for hepatitis A and E are not reported. So once again, the cause for the observed abnormalities is not established. The investigator attributed them to "changes in the diet." Results of tests for hepatitis A and E would be helpful, until which time, dili (mild and transient) cannot be completely excluded. A point against this possibility, however, is that liver tests were improving even before withdrawing the drug.

Conclusion

Based on this group of cases selected for review, no signal for hepatotoxicity is appreciated for canagliflozin at this time.

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/s/

MARGARITA V TOSSA
12/12/2012

ALLEN D BRINKER
12/12/2012

Clinical Consultation
DRUP Track Correspondence No. 384

From: Stephen Voss MD, Medical Officer DRUP

Through: Theresa Kehoe MD, Medical Team Leader DRUP
Hylton Joffe MD, MMSc, Division Director DRUP

To: Division of Metabolism and Endocrinology Products:
Jena Weber, RPM
Hyon J. Kwon, PharmD, MPH, Clinical Reviewer
Jean-Marc Guettier MD, Clinical Team Leader
Mary Parks MD, Division Director

Subject: **NDA 204042, Canagliflozin – review of bone safety data**
IND: 076479
Date of consult request: October 19, 2012

Background:
Canagliflozin (JNJ-28431754, Janssen Research and Development) is an NME oral agent for treatment of type 2 diabetes mellitus (T2DM). Canagliflozin is an inhibitor of SGLT2 (sodium-dependent glucose co-transporter 2), the major transporter responsible for renal glucose reabsorption. This inhibition results in urinary glucose excretion with reduction in plasma glucose, and potentially other benefits including reduction in body weight and fat mass, and changes in lipids. DMEP is currently evaluating NDA 204042 for canagliflozin which, if approved, would be the first in the SGLT2 inhibitor class. The PDUFA goal date is March 31, 2013.

Canagliflozin and dapagliflozin, another SGLT2 inhibitor, have demonstrated efficacy in reducing $HgbA_{1c}$, fasting and postprandial glucose, when given as monotherapy or in combination with other agents. These drugs induce an osmotic diuresis. Clinical trials of canagliflozin showed an increase in adverse reactions potentially related to volume depletion e.g. postural dizziness, orthostatic hypotension. Events of renal impairment or failure were more common in subjects with baseline moderate renal impairment or age over 65. In combination with insulin or sulfonylureas (SUs), there was an increased rate of episodes of hypoglycemia.

Bone safety has been evaluated with these SGLT2 inhibitors because of properties that may include altered renal tubule reabsorption of calcium and phosphorus, potential for altered vitamin D metabolism, tendency for weight loss, and preclinical bone findings of hyperostosis in rats with these drugs; as well as an apparent increased propensity of some diabetics for osteoporosis and/or falls (e.g. related to decreased vision, neuropathy etc.) and previous findings of increased fractures with PPARγ drugs, which may potentially be co-administered to treat T2DM.

DRUP has previously provided consultation regarding data on dapagliflozin (see consult review by Dr. M. Whitaker in DARRTS, NDA 202293, 7/18/11). Key findings of this evaluation included:

- There were no clinically significant changes in mineral metabolism (serum and urine Ca, Phos, Mg, 25-OH-vitamin D showed minimal change, PTH showed a slight increase)
- Bone turnover markers showed small inconsistent changes in bone resorption and formation
- Bone mineral density (BMD): the drug had minimal effect on mean BMD although there were outliers with positive and negative changes of ~8-12%
- The overall fracture rate was low (1.4%) and balanced between dapagliflozin and control groups
- A study of patients with moderate renal dysfunction (eGFR 30-59 mL/min) showed an apparent increase in fractures of various types with the drug, however there was no increase when subjects across all phase 2b/3 studies with moderate renal dysfunction were pooled
- Fractures were associated with various risks for falls e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state
- Dapagliflozin was associated with increased rates of hypoglycemia, hypotension, dizziness, syncope and falls, though it was not possible to directly link such events to fractures

The conclusion of this evaluation was that there was no indication that dapagliflozin has a significant adverse effect on bone, though long term data were limited at that point. DRUP is now asked to evaluate similar bone-related data for canagliflozin, submitted in NDA 204042 (original submission 5/31/12). A 4 month safety update with updated data on fractures was submitted on 10/23/12 (#0008, SD-10).

Nonclinical overview:
In rat toxicology studies, a dose-dependent increase in metaphyseal trabecular bone (hyperostosis) of sternum, femur and tibia was observed with canagliflozin treatment, which was reversible upon drug discontinuation. Reduced bone size, area and strength were also seen at higher dose, associated with decreased body weight gain at this dose. Also seen in the rats were a marked dose related increase (~10- to 18-fold) in urinary calcium excretion, and reductions in levels of PTH, 1,25-OH-vitamin D, calcitonin and markers of bone turnover (osteocalcin, CTX-1 and DPD). Rather than representing mobilization of calcium from bone, Janssen believes the increased urinary calcium results from cross-reaction of the drug with the intestinal SGLT1 glucose transporter, causing excess carbohydrate in the gut lumen which (by unclear mechanisms) results in hyperabsorption of calcium. They believe that the hyperostosis and reductions in vitamin D, PTH and bone turnover markers are secondary to this hyperabsorption of calcium. Supporting this hypothesis are the observations that diets low in carbohydrate prevented the excess calcium excretion and hyperostosis, and dietary calcium restriction also prevented the hyperostosis. In addition, studies with labeled calcium demonstrated increased enteral absorption. Lesser increases in urinary calcium (~2-to-3-fold) occurred in dogs; hyperostosis did not occur in mice or dogs.

Reviewer comment: *Increased urinary calcium, hyperostosis and reduced 1,25-OH-vitamin D and bone turnover markers also occurred with dapagliflozin in rats. For both drugs, these findings are inconsistent with clinical studies which show increased bone resorption (CTX), without increased urinary calcium excretion.*

Overview of canagliflozin clinical trials:
The ISS presents data from 40 phase 1 studies, 3 phase 2 studies and 9 phase 3 studies. Data related to calcium, phosphorus, vitamin D, PTH and bone turnover markers were evaluated in three **phase 2** studies, each of 12 week duration and with a total of 1210 subjects. Two of these (DIA2001 and TA-7284-04) were conducted in T2DM subjects, and one (OBE2001) in nondiabetic overweight/obese subjects. (The sponsor is not currently seeking the latter indication.)

There were nine **phase 3** trials of canagliflozin in T2DM, involving a total of 10,285 Type 2 diabetic adults with inadequate control. Fracture data were captured as adverse events on supplemental eCRFs in all of these studies, which include:

- 4 **placebo-controlled** studies (**DIA3005**, **DIA3002**, **DIA3006** and **DIA3012**) which differ mainly in the subjects' background diabetic therapy (diet/exercise, metformin/SU, metformin, and metformin/pioglitazone respectively), each with 52 week duration and primary analysis at 26 weeks
- 2 **active-controlled** studies (**DIA3009**, **DIA3015**) with background regimens of metformin and metformin/SU respectively, and comparator treatments of glimepiride and sitagliptin respectively; primary analysis at 1 year
- 3 studies in **special populations**, placebo-controlled, with <u>any</u> stable background regimen (including insulin):
    - **DIA3004**: patients with **moderate renal impairment** (eGFR 30-50 mL/min/1.73 m^2); 52 week duration, primary analysis at 26 weeks
    - **DIA3008**: patients with **cardiovascular disease** or at high CV risk based on risk factors; long-term study, estimated duration 4-8 years; stratified by background therapy; the largest individual study (n=4330)
    - **DIA3010**: patients at **higher risk of fracture, i.e. older age** (55-80 y/o); 104 week duration, primary analysis at 26 weeks

Enrollment criteria of these phase 3 trials included the following:
- Inclusion: in most of the trials, inadequate glycemic control was defined as $HgbA_{1c}$ of 7.0-10.0%, and fasting plasma glucose ≥ 110 mg/dL but < 270 mg/dL
- Only adults (male or female) were enrolled, mostly defined as ≥ 18 y/o (except DIA3010)
- Renal function: eGFR ≥ 60 mL/ min/1.73 m^2 was required in most studies except DIA3004 and DIA3008, and severe renal impairment (eGFR < 30 mL/min/1.73 m^2) was an exclusion for all subjects
- Subjects with other microvascular complications e.g. neuropathy or retinopathy were not excluded

DIA3010, as the phase 3 study dedicated to bone safety with measurement of bone turnover markers and BMD, had additional enrollment criteria such that subjects were older (age 55-80 y/o) and women were ≥ 3 yrs postmenopause, with the following additional exclusions:

- Treatment with a bisphosphonate, teriparatide or denosumab within 12 months
- Osteoporosis (T-score < -2.5 at any site), unless on stable treatment with estrogen replacement, SERM or calcitonin (which were allowed as concomitant drugs)
- Treatment with systemic glucocorticoids for a total of >14 days within 3 months, or likely to require such therapy during the study
- Serum 25-OH-vitamin D level ≤ 10 ng/mL
- Hypercalcemia
- Impediments to DXA: severe scoliosis or DJD of spine, spinal fusion, spine or hip implant
- Non-healed fracture, or any fracture within 12 months
- Bone metabolic disease e.g. Paget's, osteomalacia, osteopetrosis, osteogenesis imperfecta, elevation of alkaline phosphatase > 1.5 x WNL
- Rheumatoid arthritis

Demographics of these nine phase 3 studies reflects a combination of 6 studies enrolling all adults with T2DM, with mean ages of 56-58 y/o; and 3 studies involving the renal, cardiovascular and bone-safety populations, with mean ages of 69, 63 and 63 y/o respectively. Among the 9439 subjects in the long-term DS4 dataset representing 92% of phase 3 subjects, the median age at enrollment was 60 y/o, and 58% are men; 36% are enrolled in North America and 27% in Europe; 73% are white, 16% Asian and 4% black or African-American; ethnicity is 16% Hispanic. The mean BMI was 31.9 kg/m^2. The mean duration of diabetes was 9.6 years at baseline, and mean $HgbA_{1c}$ was 8.0%. At baseline, 75% of subjects were using metformin, 20% were using a sulfonylurea (SU) and 15% were using a PPARγ agent. Moderate renal impairment (< 60 mL/min/1.73m^2) was present in 13%. Less than 1% used estrogens.

All of these phase 3 studies are randomized, controlled, and double blinded. Each trial uses both of the canagliflozin (referred to as "Cana" in this review) doses intended for marketing, i.e. 100 mg and 300 mg daily, in addition to placebo and/or active control (collectively referred to as "Non-Cana"), except for DIA3015 which only uses 300 mg. Investigators and patients are instructed not to alter the background diabetic regimen unless the patient meets specific criteria related to glycemic control ("rescue therapy") or medication intolerance.

Bone safety assessments of canagliflozin studies include data related to calcium/ phosphorus/ vitamin D metabolism; markers of bone turnover; bone mineral density; and fractures.

Calcium metabolism

In the 12-week phase 2 dose-finding trial DIA2001 in T2DM subjects suboptimally controlled with metformin, there were no consistent Cana-associated changes in serum or urine calcium or serum phosphorus, and slight decreases in 25-OH-vitamin D and 1,25-

OH-vitamin D levels at higher doses. (see table below) There was a small, non-dose-dependent increase in PTH at week 3 in the Cana groups relative to placebo and sitagliptin, which returned to baseline by weeks 6 and 12 (in contrast to the reduction in PTH seen in the rats). Serum magnesium levels increased by ~10%. In two other 12-week phase 2 studies (OBE2001 and TA-7284-04) there were small increases from baseline in urine and serum phosphorus respectively, but also no change in serum or urine calcium. In TA-7284-04 there were also small decreases in 1,25-OH-vitamin D levels at week 8 which returned toward normal by week 12.

Study DIA2001 (Phase 2): Calcium-related metabolism

Table 153 Calcium, Calcium Regulating Hormones and Bone Turnover Markers: Mean Percentage Changes from Baseline to Week 12 (Study 28431754-DIA2001: Safety Analysis Set)

	PBO (N=65)	50 QD (N=64)	100 QD (N=64)	200 QD (N=65)	300 QD (N=64)	300 BID (N=64)	Sita (N=65)
Blood 1,25-Dihydroxy Vitamin D (Pmol/L)							
Mean baseline	124.4	119.5	131.4	131.4	129.1	124.6	134.3
Mean % change (SD)	-2.0 (43.5)	10.5 (59.0)	-9.3 (35.0)	-6.9 (40.4)	-16.3 (40.3)	-12.0 (42.4)	-5.0 (57.7)
Median % change	-13.3	2.6	-13.6	-11.2	-24.0	-18.0	-21.1
Blood 25-Hydroxy Vitamin D (Nmol/L)							
Mean baseline	68.2	59.1	60.2	60.6	64.8	62.3	64.1
Mean % change (SD)	-3.8 (35.8)	0.3 (37.0)	-1.7 (28.7)	-1.9 (38.9)	-9.1 (31.8)	-4.8 (30.0)	1.4 (56.9)
Median % change	-11.4	-7.0	-7.5	-8.9	-11.7	-13.4	-13.1
Blood Calcium (Mmol/L)							
Mean baseline	2.406	2.414	2.431	2.398	2.425	2.439	2.422
Mean % change (SD)	0.7 (4.5)	-0.4 (7.2)	-0.3 (3.6)	1.0 (5.4)	0.6 (4.4)	0.9 (5.2)	-0.2 (3.1)
Median % change	1.0	-0.2	0.0	0.6	0.0	0.4	-0.2
Blood Collagen Type 1 Beta Carboxy Telopeptide (Ng/Ml)							
Mean baseline	0.3500	0.3605	0.3381	0.3226	0.3218	0.3634	0.3424
Mean % change (SD)	9.2 (23.6)	22.5 (51.0)	29.9 (38.1)	36.6 (47.1)	35.2 (50.1)	35.0 (40.9)	3.3 (30.1)
Median % change	2.4	7.3	22.7	29.5	28.5	35.6	0.0
Blood Parathyroid Hormone (Pmol/L)							
Mean baseline	4.12	4.37	4.61	4.48	3.99	4.25	4.09
Mean % change (SD)	13.6 (50.6)	19.2 (49.9)	12.6 (46.4)	1.6 (37.2)	7.9 (39.3)	-1.0 (29.3)	9.5 (37.6)
Median % change	0.0	12.5	3.9	-11.4	0.0	-3.0	0.0
Blood Phosphate (Mmol/L)							
Mean baseline	1.149	1.209	1.160	1.117	1.223	1.197	1.168
Mean % change (SD)	4.7 (13.3)	-0.2 (13.6)	1.6 (12.1)	7.5 (14.0)	1.5 (14.8)	6.3 (14.1)	1.4 (12.2)
Median % change	4.0	-2.1	2.8	6.6	2.4	5.7	-0.9
Urine Calcium/Creatinine Ratio (Mg/mg)							
Mean baseline	0.1949	0.1926	0.2102	0.1794	0.2027	0.1629	0.1808
Median % change	-4.2	-4.0	0.0	21.3	9.2	22.7	8.0
Urine N-Telopeptide/Creatinine Ratio (Nmolbce/Mmol Cr)							
Mean baseline	22.99	25.09	24.90	29.75	29.45	25.23	21.18
Median % change	12.1	-1.3	31.7	1.4	22.5	11.4	-12.4

Source: ISS p. 332

Reviewer comment: *These findings are generally consistent with dapagliflozin studies, where there were minimal, clinically insignificant changes in serum calcium, phosphorus, magnesium, and 25-OH-vitamin D, and small increases in PTH that were clinically insignificant.*

In the pooled dataset of all placebo-controlled phase 3 trials (DS1), mean serum calcium levels increased minimally (0.6-1.1%) from baseline. There was a somewhat larger increase in mean serum phosphate: 3.6%, 5.1% and 1.5% increase from baseline to 26 weeks for canagliflozin 100 mg, 300 mg, and placebo groups respectively. In study DIA3010, there were increases of 8.3% and 10.8% in serum magnesium relative to placebo at 26 weeks, but minimal change in calcium or phosphorus.

In DIA3004, the phase 3 study of 272 T2DM subjects with moderate renal impairment, there were slight increases from baseline to week 26 in mean serum calcium, phosphorus and magnesium of 1.3%, 7.8% and 14.6% respectively for the larger (300 mg) Cana dose,

with lesser increases for 100 mg and no change with placebo. Mean serum PTH in this study decreased by 10.3% and 16.1% compared to placebo for 100 mg and 300 mg respectively, however the Cana groups had higher levels at baseline and the differences between treatment groups were not significant statistically. There were moderate increases in 25-OH-vitamin D and slight decreases in 1,25-OH-vitamin D relative to placebo.

Bone turnover markers
In two phase 1 studies (diabetic and non-diabetic subjects), there were no changes after 2 weeks of treatment with Cana on markers of bone resorption (NTX and DPD) or formation (osteocalcin and BSAP).

In the 12-week phase 2b study DIA2001 (420 male and female T2DM subjects), as per the above Table 153, there were 22-36% increases from baseline that were apparent by week 3 and persisted in the bone resorption marker CTX, compared to 9% with placebo and 3% with sitagliptin (unlike rats which exhibited decreases in CTX). Other markers (NTX, TRACP, BSAP, osteocalcin, P1NP) did not show consistent changes. Similar increases in CTX occurred in other 12-week studies in obese, non-diabetic subjects (OBE2001) and Japanese subjects (TA-7284); the latter study also showed smaller increases in NTX, and decreases in BSAP.

In the phase 3 bone-safety study DIA3010 (total N=714), bone turnover markers were measured at baseline and after 26 weeks of treatment. Consistent with the phase 2 studies, there were LS mean increases from baseline in CTx at 26 weeks of 28.8% and 36.6% with Cana 100 mg and 300 mg respectively, compared to 11.8% with placebo – differences that were statistically significant. There were smaller, non-significant decreases in P1NP with Cana compared to placebo. (see ISS Tables 155 and 156, next page)

Table 155 Serum Collagen Type 1 Beta-Carboxy-Telopeptide (beta-CTx): Percent Change From Baseline to Week 26 - Regardless of Rescue Medication (Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Serum collagen type 1 beta-carboxy-telopeptide			
Value at Baseline (µg/L)			
N	188	211	203
Mean (SD)	0.35 (0.189)	0.35 (0.177)	0.34 (0.165)
Value at Week 26 (µg/L)			
N	188	211	203
Mean (SD)	0.36 (0.204)	0.42 (0.219)	0.44 (0.227)
% Change from Baseline			
N	188	211	203
Mean (SD)	8.6 (49.7)	25.8 (44.7)	34.0 (57.5)
LS Mean (SE)	11.8 (4.7)	28.8 (4.8)	36.6 (4.9)
Diff. (%) of LS Means (SE)(minus Placebo)		17.1 (5.0)	24.9 (5.0)
95% CI [a]		(7.3;26.9)	(15.0;34.8)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline beta-CTx.

Note: The table includes only the subjects who had both baseline and post baseline beta-CTx.

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Table 156 Serum Propeptide Amino-Term Type 1 Procollagen (P1NP): Percent Change From Baseline to Week 26 - Regardless of Rescue Medication (Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Serum propeptide amino-term type 1 procollagen			
Value at Baseline (µg/L)			
N	194	222	206
Mean (SD)	34.42 (15.695)	33.68 (17.472)	33.98 (12.703)
Value at Week 26 (µg/L)			
N	194	222	206
Mean (SD)	35.94 (22.394)	33.05 (14.498)	33.22 (12.700)
% Change from Baseline			
N	194	222	206
Mean (SD)	6.8 (58.1)	2.0 (26.0)	0.4 (23.8)
LS Mean (SE)	8.4 (3.5)	2.7 (3.6)	1.5 (3.7)
Diff. (%) of LS Means (SE)(minus Placebo)		-5.7 (3.8)	-6.9 (3.8)
95% CI [a]		(-13.1;1.7)	(-14.3;0.6)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline P1NP.

Note: The table includes only the subjects who had both baseline and post baseline P1NP.

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Source: ISS

Bone mineral density is measured in this one phase 3 study, **DIA3010**, which was designed to evaluate bone safety. As such, the study enrolled older T2DM adults (age 55-80 y/o) including females who were at least 3 years post menopause, and there were several exclusion criteria related to disorders and/or medications potentially affecting bone (bisphosphonates, teriparatide, denosumab, glucocorticoids for >2 weeks). Subjects could be on any stable regimen of oral and/or injectable antidiabetic medications for at least 3 months prior to screening, or 6 months if pioglitazone was included (rosiglitazone

was not allowed). Following stratification for baseline lumbar spine T-score category (< -1.5, ≥ -1.5) and PPARγ use, subjects were randomized 1:1:1 to receive Cana 100 mg, Cana 300 mg or placebo for 2 years. If subjects met criteria for glycemic rescue during the study, the only change in background regimen not allowed was the addition of pioglitazone or change in dose thereof.

In this study, DXA of the lumbar spine, total hip, femoral neck and forearm (1/3 radius) is conducted at weeks 26, 52 and 104. The NDA includes only the week 26 data which constitutes the primary safety endpoint. The study is ongoing and the 52-week and 104-week data will be submitted in a later report. A central DXA facility (Bioclinica Inc.) is used for instrument calibration and central interpretation of the data.

[As a secondary endpoint, BMD will also be evaluated in this study using QCT of the spine and hip at week 52, in a subset of subjects (~50 per arm), in order to assess BMD changes specific to trabecular and cortical bone, geometric properties, and material properties using finite element analysis (FEA). These data are not yet submitted.]

It was calculated that 156 subjects per treatment group in this study would exclude a decline in lumbar spine BMD of > 0.9%. This is the lower bound of the 95% CI for a 2-sided comparison, assuming a standard deviation of 4.05% (derived from literature) for percent change from baseline in LS-BMD in placebo recipients over 2 years, with type I error rate of 0.05.

A total of 716 subjects were randomized, and 88% completed the 26 week primary analysis period (91% of Cana recipients and 83% of placebo recipients). The median age was 63 y/o; 56% were male; 77% were white, 9% were Asian and 8% were black or African-American; ethnicity was 15% Hispanic. Mean BMI was 31.6 kg/m^2. At baseline, 12.2% of subjects were on a PPARγ agent. Baseline T-score was ≥ -1.5 in 77% of subjects. Only one subject (#101517) took corticosteroid therapy for greater than 14 days during the study. Seven subjects were using estrogens, and 2 were using SERMs, at baseline.

The Applicant's analysis of 26-week BMD findings from study DIA3010 at the 4 skeletal sites are summarized in the Applicant's Tables 37-40 on the following pages, taken from pp. 138-139 of the CSR. Lumbar spine BMD showed small placebo-subtracted changes from baseline of +0.2% for Cana 100 mg and -0.3% for Cana 300 mg. The 1/3 radius BMD showed small placebo-subtracted declines of -0.3% and -0.4% for Cana 100 mg and Cana 300 mg respectively. The hip findings were somewhat inconsistent and also small: placebo-subtracted increases at femoral neck (+0.3% and +0.4%) but decreases at total hip (-0.4% and -0.5%) for Cana 100 mg and 300 mg respectively. Among these various changes, the only ones to achieve statistical significance between treatment groups were those at total hip (i.e. declines).

Table 37: Lumbar Spine Measurement: Percent Change From Baseline to Week 26 - Regardless of Rescue Medication

(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Lumbar spine corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	185	206	192
Mean (SD)	1.15687 (0.195706)	1.16170 (0.182599)	1.17986 (0.198626)
Value at Week 26 (g/cm^2)			
N	185	206	192
Mean (SD)	1.15956 (0.197824)	1.16622 (0.188740)	1.17984 (0.204915)
% Change from Baseline			
N	185	206	192
Mean (SD)	0.3 (2.9)	0.4 (3.0)	-0.0 (2.9)
LS Mean (SE)	0.5 (0.3)	0.7 (0.3)	0.2 (0.3)
Diff. (%) of LS Means (SE)(minus Placebo)		0.2 (0.3)	-0.3 (0.3)
95% CI[a]		(-0.4;0.8)	(-0.9;0.3)

[a] Pairwise comparison: CIs were based on an ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Lumbar Spine Corrected BMD Measurement.

Note: The table includes only the subjects who had both baseline and post baseline Lumbar Spine Corrected BMD measurements.

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Table 38: Distal Forearm: Percent Change From Baseline to Week 26 - Regardless of Rescue Medication

(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Distal forearm corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	187	208	187
Mean (SD)	0.84697 (0.128361)	0.82073 (0.131579)	0.84375 (0.147968)
Value at Week 26 (g/cm^2)			
N	187	208	187
Mean (SD)	0.84627 (0.132586)	0.81778 (0.133452)	0.84000 (0.151366)
% Change from Baseline			
N	187	208	187
Mean (SD)	-0.1 (2.9)	-0.4 (3.1)	-0.5 (3.7)
LS Mean (SE)	-0.5 (0.3)	-0.7 (0.3)	-0.8 (0.3)
Diff. (%) of LS Means (SE)(minus Placebo)		-0.3 (0.3)	-0.4 (0.3)
95% CI[a]		(-0.9;0.4)	(-1.0;0.3)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Distal Forearm Corrected BMD measurement.

Note 1: Distal forearm: region of interest, 1/3 radius (33% radius).

Note 2: The table includes only the subjects who had both baseline and post baseline Distal Forearm Corrected BMD measurements.

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Table 39: Femoral Neck: Percent Change From Baseline to Week 26 - Regardless of Rescue Medication
(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Femoral neck corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	183	209	190
Mean (SD)	0.89590 (0.148117)	0.90451 (0.158234)	0.91705 (0.155647)
Value at Week 26 (g/cm^2)			
N	183	209	190
Mean (SD)	0.89164 (0.149695)	0.90270 (0.154215)	0.91538 (0.153458)
% Change from Baseline			
N	183	209	190
Mean (SD)	-0.5 (3.2)	-0.1 (3.3)	-0.1 (3.5)
LS Mean (SE)	-1.0 (0.3)	-0.7 (0.3)	-0.6 (0.3)
Diff. (%) of LS Means (SE)(minus Placebo)		0.3 (0.3)	0.4 (0.3)
95% CI[a]		(-0.3;1.0)	(-0.3;1.1)

[a] Pairwise comparison: CIs were based on an ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Femur Neck Corrected BMD measurement.

Note: The table includes only the subjects who had both baseline and post baseline Femoral Neck Corrected BMD measurements.

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Table 40: Total Hip: Percent Change From Percent Baseline to Week 26 - Regardless of Rescue Medication
(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Total hip corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	183	209	190
Mean (SD)	1.03454 (0.140822)	1.04628 (0.147847)	1.05251 (0.148493)
Value at Week 26 (g/cm^2)			
N	183	209	190
Mean (SD)	1.03342 (0.142058)	1.04057 (0.146836)	1.04587 (0.148591)
% Change from Baseline			
N	183	209	190
Mean (SD)	-0.1 (1.9)	-0.5 (2.1)	-0.6 (2.1)
LS Mean (SE)	-0.5 (0.2)	-0.9 (0.2)	-1.0 (0.2)
Diff. (%) of LS Means (SE)(minus Placebo)		-0.4 (0.2)	-0.5 (0.2)
95% CI[a]		(-0.8;-0.0)	(-0.9;-0.1)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Total Hip Corrected BMD measurement.

Note: The table includes only the subjects who had both baseline and post baseline Total Hip Corrected BMD measurements.

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Source: DIA3010 CSR

Population subgroups of gender, age group and baseline eGFR for lumbar spine BMD were prespecified. (see table) In each subgroup, changes from baseline and relative to placebo for both Cana groups were small and not statistically significant.

Study DIA3010: Lumbar Spine BMD, percent changes at week 26 by subgroups

	Placebo	Cana 100 mg	Cana 300 mg
Males, n	113	109	108
Baseline, g/cm^2	1.186	1.212	1.232
Week 26, mean % change	+0.10	+0.74	+0.03
Females, n	72	97	84
Baseline, g/cm^2	1.111	1.105	1.113
Week 26, mean % change	+0.45	-0.04	-0.04
Age < 65 y/o, n	114	119	121
Baseline, g/cm^2	1.141	1.157	1.159
Week 26, mean % change	+0.74	+0.52	+0.08
Age ≥ 65 y/o, n	71	87	71
Baseline, g/cm^2	1.182	1.167	1.215
Week 26, mean % change	-0.55	+0.21	-0.13
eGFR < 90, n	146	159	140
Baseline, g/cm^2	1.164	1.156	1.186
Week 26, mean % change	+0.25	+0.41	-0.02
eGFR ≥ 90, n	39	47	52
Baseline, g/cm^2	1.130	1.181	1.163
Week 26, mean % change	+0.15	+0.33	+0.04
Source: DIA3010 CSR pp. 1193-1198			

The Applicant conducted additional post-hoc analyses of the interaction of baseline eGFR and BMD changes, by eGFR tertile (≤ 69, 70-84, and >84 mL/min/1.73 m^2). (see table) None of these tertile subgroups showed a significant treatment-related difference in BMD changes at any of the 4 skeletal sites, and reduced eGFR was not associated with adverse BMD changes. (Note that baseline eGFR ≤ 50 was an exclusion criterion for this study.)

Study DIA3010: BMD, mean percent changes at week 26 by eGFR tertiles*

	Placebo	Cana 100 mg	Cana 300 mg
Lumbar spine			
eGFR < 69	+0.1	+0.9	+0.3
eGFR 70-84	+0.5	0.0	-0.4
eGFR >84	+0.1	+0.2	-0.1
Total hip			
eGFR < 69	-0.1	-0.4	-0.5
eGFR 70-84	0.0	-0.6	-0.7
eGFR >84	-0.2	-0.5	-0.7
Femoral neck			
eGFR < 69	-0.3	+0.4	+0.1
eGFR 70-84	-0.4	-0.3	+0.3
eGFR >84	-0.7	-0.4	-0.6
1/3 radius			

eGFR < 69	-0.3	-0.7	-0.6
eGFR 70-84	-0.3	-0.4	-1.1
eGFR >84	+0.4	+0.1	+0.2
* N= 241, 247 and 226 for eGFR < 69, 70-84 and > 84 tertiles respectively			

There were 12.2% of DIA3010 subjects on a PPARγ agent at baseline. As this component of therapy was to remain unchanged throughout the study, and this subgroup was small, no analysis was done for the subgroup. The use of PPARγ agents was not a significant term in the model used to analyze lumbar spine BMD.

Reviewer comment: *In summary as shown in the Applicant's table below, BMD changes over 26 weeks with canagliflozin were small and non-significant at lumbar spine and 1/3 radius. The total hip BMD decline was statistically significant relative to placebo, however these changes (-0.4% and -0.5% with Cana 100 mg and 300 mg respectively) were modest and in the opposite direction to those at femoral neck. Age and gender subgroups showed no significant differences in lumbar spine BMD changes; renal function subgroups did not differ from each other at any skeletal site. None of these BMD findings appear likely to be of significance clinically, however additional DXA data at weeks 52 and 104 will be helpful, as will QCT data.*

Summary: Percent Change from Baseline to Week 26 - Regardless of Rescue Medication for Bone Safety
(Study 28431754-DIA3010: Safety Analysis Set)

Endpoints – corrected BMD measurement % change	CANA 100 mg (Placebo-Subtracted) LS Mean (95% CI)	CANA 300 mg (Placebo-Subtracted) LS Mean (95% CI)
Lumbar spine	0.2 (-0.4; 0.8)	-0.3 (-0.9; 0.3)
Total hip	-0.4 (-0.8; 0.0)	-0.5 (-0.9; -0.1)
Femoral neck	0.3 (-0.3; 1.0)	0.4 (-0.3; 1.1)
Distal forearm	-0.3 (-0.9; 0.5)	-0.4 (-1.0; 0.3)

Note: The least squares (LS) mean is presented with associated CI based on ANCOVA models with terms for treatment, sex, T-score of lumbar spine (<-1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and adjusting for the baseline value as a covariate.

Fractures

Investigators gathered data on all suspected clinical fractures across all phase 2 and 3 studies using a supplemental eCRF which recorded the fracture date and history of the event, level of trauma and skeletal location. This information, including additional review of radiographic images as needed, is evaluated by an independent, treatment-blinded Fracture Adjudication Committee (FAC), consisting of experienced radiologists employed by Synarc, the imaging vendor. The FAC confirmed that a fracture had occurred and classified it by location and one of the following:

- **High Trauma Fracture**: fractures resulting from severe trauma such as motor vehicle crashes, being struck by a vehicle or other fast-moving projectile, or falls from greater than standing height (e.g. falls off a ladder or other raised surface, not including stairs)
- **Low Trauma Fracture**: fractures due to falls from standing height or less; falls on stairs, steps, or curbs; moderate trauma other than a fall (e.g. collisions with objects during normal activities); and minimal trauma other than a fall (e.g. turning over in bed)
- **Pathological Fracture**: fractures occurring in an area that is weakened by another disease process such as a tumor, metastatic cancer of the bone, infection, inherited bone disorders, etc.

- **Stress Fracture**: identifiable fractures caused by repetitive stress
- **Other Fracture**: fractures that cannot be attributable to the definitions above

Reviewer comment: *The intent of the high-trauma/ low-trauma classification, presumably, was to differentiate fractures that were unlikely to be related to any compromise in bone strength (high-trauma) from those that were likely to be so related (low-trauma). However, trauma history may be misleading in some cases. In particular, fractures of metacarpals, metatarsals and phalanges are generally considered to have no relationship to bone fragility, yet under the above definitions may have been classified as low-trauma. Conversely, many fractures associated with significant trauma occur in part because of underlying fragility. Thus in osteoporosis trials, fractures of vertebrae, hip, forearm and humerus (other than pathologic) are generally considered potentially relevant to bony integrity regardless of trauma severity, and fractures of hand, foot, skull or face are typically disregarded. Because this NDA did not include any information regarding the adjudication findings other than overall tabulations of the categories, the relevance of the trauma classifications used is unclear.*

Phase 3 safety data, including fracture data, were pooled for analysis in the ISS. Because the 9 phase 3 studies examined different diabetic populations (6 represented general T2DM, and one each represented subjects with moderate renal dysfunction, elevated CV risk, and older age/increased fracture risk), an effort was made to have each study's representation in the dataset evenly distributed ~1:1:1 between Cana 100 mg: Cana 300 mg: Non-Cana control. Thus, one study (DIA3015) without a Cana 100 mg group and a small substudy of another (DIA3005) without a control group were excluded. The Non-Cana control groups, representing placebo, glimepiride or sitagliptin depending on the study, were combined for comparison for the same reason.

Reviewer comment: *There is no evidence that glimepiride or sitagliptin have any significant effect on BMD or fractures, therefore it appears reasonable to combine these groups with placebo for the overall comparison of fractures.*

These data, from 8 of the 9 phase 3 studies, were pooled for analysis in the ISS, and fracture data are included in a long term (designated as "DS4") ADAE dataset. At the 1/31/12 cutoff date for ISS data, all 8 of these studies were ongoing, and 159 subjects with fractures had been reported. The 4 Month Safety Update extends the cutoff date to 7/1/12, by which time 44 additional subjects with fractures had been reported. As of that date, the length of exposure exceeded 6, 12, 18 and 24 months for 88%, 79%, 40% and 12% of the 10,285 phase 3 study subjects.

Both the ISS and 4-Month Safety Update include Applicant analysis of cumulative fractures from these 8 studies. These analyses are based on all fractures occurring post-randomization in this DS4 dataset, including those on treatment and for an unlimited length of time following end of treatment. Summary data from the FAC adjudications were also analyzed.

The long term DS4 ADAE dataset includes 9439 subjects, who were randomized to Cana 100 mg (N=3092), Cana 300 mg (N=3085), or Non-Cana (N=3262). The Non-Cana

(control) group treatment varies by study; overall this group represents 2412 subjects (74%) randomized to placebo; 484 subjects (15%) randomized to glimepiride (titrated to 1-8 mg) and 366 subjects (11%) randomized to sitagliptin 100 mg. The Non-Cana group is slightly larger than the two Cana groups because randomization in one study, DIA3006, was 2:2:2:1 to Cana 100 mg: Cana 300 mg: sitagliptin 100 mg: placebo, whereas in the other studies randomization was 1:1:1.

These 9439 phase 3 subjects were 58% male with mean age of 60 y/o. As noted in the following table, nearly half the subjects, and more than half the fractures, were from the largest study, DIA3008, which enrolled somewhat older subjects (mean age 63 y/o) with increased cardiovascular risk. The bone safety study, DIA3010, had fewer fractures compared to DIA3008 and DIA3009, as it is smaller and was initiated 5-8 months later. Collectively at the time of the ISS, there were 189 fracture events, in 159 subjects, reported in the DS4 dataset to have occurred following randomization, which were evenly distributed among the Cana 100 mg, Cana 300 mg and Non-Cana groups.

All phase 3* fracture events post-randomization, by study and treatment group (DS4, ISS, prior to adjudication)

Study	Population	Mean age	# subjects randomized in study	# of fracture events*	Cana 100 mg (n=3092)	Cana 300 mg N=3085)	Non-Cana** (N=3262)
DIA3005	General T2DM	56	587	6	1	4	1
DIA3002		58	469	4	0	2	2
DIA3006		56	1284	12	4	3	5*
DIA3012		57	344	3	1	1	1
DIA3009		57	1452	31	10	7	14*
DIA3004	Renal insuff	69	272	7	2	2	3
DIA3008	Cardiovascular	63	4330	116	42	36	33
DIA3010	Increased fracture risk	63	716	15	5	6	4
Total				**189**	**65**	**61**	**63***

* In the only phase 3 study not included in this dataset, DIA3015, there were 2 fractures with Cana 300 mg and 1 fracture with active control (sitagliptin).
** Non-Cana fractures represent placebo with the following exceptions: Study DIA3006 – 4 fractures occurred with sitagliptin 100 mg, and 1 fracture with placebo; Study DIA3009 – 14 fractures occurred with glimepiride
Source: ISS and DS4 ADAE dataset

Although the post-randomization fracture events in the ISS were overall about even among the treatment groups, the subject incidence was higher in the Cana groups: 58 (1.9%) and 54 (1.8%) in the Cana 100 mg and Cana 300 mg groups respectively, and 47 (1.4%) in the Non-Cana group.

Reviewer comment: *The Non-Cana group had fewer subjects with fractures, but about the same number of fracture AEs, relative to the two Cana groups. Thus, this group had more subjects (11) with multiple fracture AEs, relative to the Cana groups (8 and 6). All except two of these Non-Cana subjects had fractures of different bones on the same day, most notably a 63 y/o man with a motor vehicle accident resulting in fractures of scapula,*

clavicle and 5 ribs, each counted as a separate AE. Others included a 56 y/o man who fell from stairs resulting in fractures of R fibula and R calcaneus, and a 76 y/o man who incurred fractures of C-6 and C-7 in a motor vehicle accident. Most of the other subjects with >1 fracture, both Cana and Non-Cana, also appear to have experienced significant trauma. Therefore, it is unlikely that the treatment group difference in number of subjects with multiple fractures has any implications regarding bone fragility.

ISS fracture events adjudicated as high-trauma were approximately even across treatment groups (0.4%, 0.3% and 0.3% respectively), but low-trauma events were more common with Cana 100 mg or 300 mg (each 1.3%) relative to control (1.0%). The Applicant's ISS analysis found no statistical differences in these comparisons, nor when the Cana 100 mg and 300 mg groups were pooled together for comparison to Non-Cana.

In the 4-Month Safety Update, with 44 additional subjects with fractures, the Applicant updated these analyses (see Applicant's Table 29, next page). The additional fractures were somewhat more numerous with the test drug: 18, 16 and 10 additional subjects from the Cana 100 mg/ Cana 300 mg/ Non-Cana groups respectively. Thus, the updated difference in fracture incidence between the combined Cana groups (2.4%) and Non-Cana subjects (1.7%) approached statistical significance. As the Applicant notes, there were more dropouts in the Non-Cana groups, therefore the median duration of exposure was greater in the combined Cana groups relative to Non-Cana (73 vs. 66 weeks). Thus, the time-adjusted incidence rates of 18.11 vs. 14.16 fractures per 1000 person years of exposure for Cana and Non-Cana respectively were somewhat closer than the incidence rates not so adjusted. The treatment group differences in incidence of positively adjudicated fractures (2.2%, 2.0% and 1.6% respectively) were not statistically significant.

The rate of low trauma fractures continued, in the 4-Month Safety Update, to be numerically higher in the Cana groups (1.6% each, vs. 1.2% for Non-Cana), though this difference was not statistically significant. In a time to event analysis of all low trauma events in the Safety Update (adjudicated and otherwise), the curves of the Cana and Non-Cana treatment groups appear to separate even as early as 12 weeks. (see Applicant's Figure 2 below)

Table 29 Post Randomization Fracture Adverse Events by Fracture Type - Regardless of Use of Rescue Medication (JNJ-28431754 Four Month Safety Update: Safety Analysis Set) (DS3-LT2)

Fracture Type	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)	Cana 100 mg Minus ---All Non-Cana--- Diff[a]	95%CI[b]	Cana 300 mg Minus ---All Non-Cana--- Diff[a]	95%CI[b]	All Cana Minus ---All Non-Cana--- Diff[a]	95%CI[b]
Total no. subjects with adverse events[c]	76 (2.5)	70 (2.3)	146 (2.4)	57 (1.7)	0.7	(-0.0; 1.4)	0.5	(-0.2; 1.2)	0.6	(0.0; 1.2)
Incidence rate per 1000 person-years exposure (SE)[d]	18.65 (2.15)	17.56 (2.11)	18.11 (1.50)	14.16 (1.89)	4.5	(-1.14; 10.10)	3.4	(-2.17; 8.95)	3.9	(-0.79; 8.68)
Total no. subjects with Adjudicated Fracture Type[e]	68 (2.2)	61 (2.0)	129 (2.1)	53 (1.6)	0.6	(-0.1; 1.3)	0.4	(-0.3; 1.0)	0.5	(-0.1; 1.0)
High Trauma	15 (0.5)	12 (0.4)	27 (0.4)	11 (0.3)	0.1	(-0.2; 0.5)	0.1	(-0.3; 0.4)	0.1	(-0.2; 0.4)
Impact Unknown	1 (<0.1)	0	1 (<0.1)	0	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.0)	0.0	(-0.0; 0.1)
Low Trauma	51 (1.6)	48 (1.6)	99 (1.6)	38 (1.2)	0.5	(-0.1; 1.1)	0.4	(-0.2; 1.0)	0.4	(-0.1; 0.9)
Pathological	0	1 (<0.1)	1 (<0.1)	0	0.0	(-0.0; 0.0)	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.1)
Possible Unknown Trauma	0	1 (<0.1)	1 (<0.1)	0	0.0	(-0.0; 0.0)	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.1)
Stress	1 (<0.1)	0	1 (<0.1)	3 (<0.1)	-0.1	(-0.2; 0.1)	-0.1	(-0.2; 0.0)	-0.1	(-0.2; 0.1)
Unknown	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	-0.0	(-0.1; 0.1)	0.0	(-0.1; 0.1)	-0.0	(-0.1; 0.1)

[a] Denotes the difference in the incidence rate or the difference in proportion of subjects with the adverse event

[b] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[c] Fracture adverse events based upon a prespecified subset of preferred terms from a MedDRA query listed in the SAP.

[d] Exposure adjusted incidence rates are per 1000 person-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total person-year exposure for all safety subjects in each treatment group). SE denotes the standard error of the incidence rates defined as incidence rate divided by the square root of the total number of subjects with the adverse event - 1.

[e] Adjudicated fracture type for confirmed fractures by the FAC (note that events not confirmed as a fracture or without information available to the FAC are excluded).

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence Is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of use of rescue medication.

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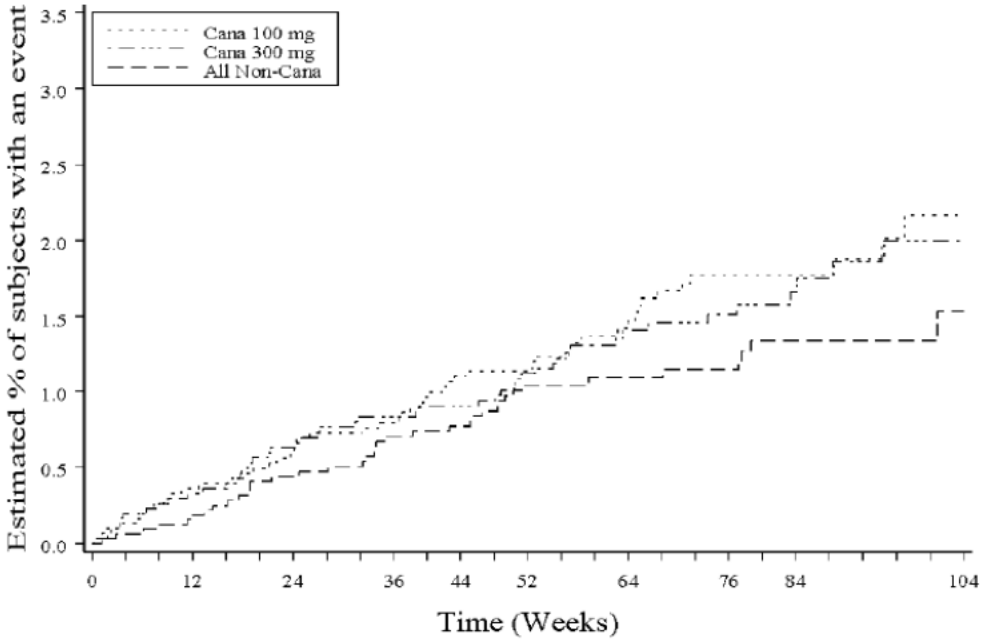
Source: 4-Month Safety Update, p. 58

Figure 2 **Kaplan-Meier Plot of Time To the First Post Randomization Low Trauma Fracture Adverse Event (JNJ-28431754 Four Month Safety Update: Safety Analysis Set) (DS3-LT2)**



No. Subjects at Risk

Cana 100 mg	3092	3042	2983	2931	2882	2840	2021	1621	1166	421
Cana 300 mg	3085	3020	2940	2870	2844	2801	1983	1601	1125	413
All Non-Cana	3262	3192	3095	3011	2964	2877	1932	1537	1113	413

Source: 4-Month Safety Update, p. 62

The Applicant's analysis of fractures by adjudicated skeletal location and trauma category demonstrated that the treatment-group disparity is mainly confined to low-trauma upper limb fractures, and to a lesser extent spine fractures, with little difference in lower limb, pelvis or rib fractures:

Subject incidence of adjudicated post-randomization fracture events by skeletal region and trauma classification (Phase 3, 4-Month Safety Update)

Number of subjects with indicated fracture region	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total adjudicated-positive	68 (2.2)	61 (2.0)	129 (2.1)	53 (1.6)
All sites/ Low trauma	51 (1.6)	48 (1.6)	99 (1.6)	38 (1.2)
Lower limb/ All	25 (0.8)	25 (0.8)	50 (0.8)	29 (0.9)
Lower limb/ Low trauma	20 (0.6)	18 (0.6)	38 (0.6)	22 (0.7)
Upper limb/ All	**28 (0.9)**	**27 (0.9)**	**55 (0.9)**	**17 (0.5)**
Upper limb/ Low trauma	**22 (0.7)**	**22 (0.7)**	**44 (0.7)**	**11 (0.3)**
Spine/ All	7 (0.2)	2 (0.1)	9 (0.1)	2 (0.1)
Spine/ Low trauma	5 (0.2)	1 (<0.1)	6 (0.1)	0
Thoracic cage/ All	9 (0.3)	9 (0.3)	18 (0.3)	7 (0.2)
Thoracic cage/ Low trauma	5 (0.2)	7 (0.2)	12 (0.2)	5 (0.2)
Pelvis	2 (0.06)	0	2 (<0.1)	1 (<0.1)

Source: 4-Month Safety Update Tables 30 and 31

The DS4 dataset includes all fractures, including large numbers of hand/finger and foot/toe fractures. These were somewhat more numerous in the Cana groups relative to Non-Cana: 15 vs. 3 subjects with hand/finger fractures, and 7 vs. 2 subjects with toe fractures. As noted previously, such fractures are generally recognized as having no relationship to bone fragility, as are fractures of skull, facial bones, scapula and patella; it is unclear how fractures at these sites were handled in the adjudications. Therefore this reviewer examined, from this ISS DS4 dataset, all 131 post-randomization fracture AEs involving other sites, i.e. bones with which a fracture may indicate a component of fragility, even in the context of some trauma. These included fractures of vertebrae, pelvis, ribs, clavicle, upper extremity (shoulder, humerus, radius, ulna, wrist) and lower extremity (hip, femur, tibia, fibula, ankle). As noted in the table below, the imbalance in upper extremity fractures persists, though for lower limb fractures there is the opposite i.e. a preponderance in the Non-Cana group. (NOTE: These data are from the dataset, which has no information regarding adjudications or high-trauma vs. low-trauma status.)

Subject incidence of post-randomization fractures by skeletal region, excluding non-fragility sites* (Phase 3, ISS)

Number of subjects Preferred Term	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total	**43 (1.39)**	**37 (1.20)**	**80 (1.29)**	**36 (1.10)**
Lower limb	**9 (0.29)**	**11 (0.36)**	**20 (0.32)**	**16 (0.49)**
Hip fracture	0	2	2	3
Femoral neck fracture	1	1	2	0
Tibia fracture	1	2	4	0
Fibula fracture	2	0	2	3
Ankle fracture	2	5	7	8
Lower limb fracture	3	0	3	1
Other**	1	1	2	1
Upper limb	**17 (0.55)**	**16 (0.52)**	**33 (0.53)**	**9 (0.28)**
Humerus fracture	4	7	11	2
Radius fracture	3	2	5	4
Ulna fracture	2	0	2	0
Wrist fracture	6	3	9	2
Upper limb fracture	2	4	6	1
Spine (thoracic/lumbar)	**6 (0.19)**	**1 (0.1)**	**7 (0.11)**	**1 (0.1)**
Spine (cervical, sacrum, coccyx)	2	0	2	1
Ribs/clavicle/sternum	7	10	17	7
Pelvis	1	0	1	2

Source: DS4 ADAE dataset (ISS)
* Excludes fractures of hand/fingers, foot/toes, skull, facial bones, scapula and patella
** Includes one each of Pathological fracture (verbatim = spontaneous fracture of right tibia/fibula); Fracture displacement (Distal right tibial posterior malleolar minimally); and Periprosthetic fracture (left femur periprosthetic fracture)

Reviewer comment: *The treatment difference in upper extremity fractures does not appear to be statistically significant. However even with this large number of subjects, it*

is not clear that the data have sufficient power to rule out a modest increase in these relatively infrequent events. As the Applicant notes, there is clearly no additional effect with increasing dose. Some of the fractures that appear to be increased are of types often indicative of reduced bone density, e.g. humerus, wrist and spine. Morphometric (i.e. asymptomatic) vertebral fractures, the most common manifestation of osteoporosis, were not evaluated in these studies, however it may be notable that back pain was reported by 5.1%, 5.5% and 6.4% of phase 3 subjects receiving Non-Cana, Cana 100 mg and Cana 300 mg respectively.

The above table was derived from the ISS dataset. The 4-Month Safety Update did not include an updated dataset, however did tabulate fractures by preferred term. In comparison to the ISS data in the above table, there is a net of one additional upper extremity fracture in the Cana 100 mg, no change in the Cana 300 mg, and two additional wrist fractures in the Non-Cana group, thus somewhat less disparity between the groups in upper extremity fractures.

Phase 3 subject incidence of fractures post-randomization, by skeletal site and treatment group (DS4, 4-Month Safety Update)

Preferred term	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Ankle fracture	4 (0.1)	6 (0.2)	10 (0.2)	8 (0.2)
Cervical vertebral fx	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Clavicle fracture	1 (<0.1)	2 (0.1)	3 (<0.1)	1 (<0.1)
Compression fracture	0	0	0	1 (<0.1)
Femoral neck fx	3 (0.1)	1 (<0.1)	4 (0.1)	0
Femur fracture	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Fibula fracture	2 (0.1)	0	2 (<0.1)	4 (0.1)
Foot fracture	10 (0.3)	13 (0.4)	23 (0.4)	11 (0.3)
Fracture displacement	2 (0.1)	1(<0.1)	3 (<0.1)	0
Fractured coccyx	1 (<0.1)	0	1 (<0.1)	0
Fractured sacrum	1 (<0.1)	0	1 (<0.1)	0
Hand fracture	8 (0.3)	8 (0.3)	16 (0.3)	5 (0.2)
Hip fracture	0	2 (0.1)	2 (<0.1)	2 (0.1)
Humerus fracture	3 (0.1)	7 (0.2)	10 (0.2)	2 (0.1)
Lower limb fracture	3 (0.1)	0	3 (<0.1)	1 (<0.1)
Lumbar vertebral fx	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Patella fracture	1 (<0.1)	0	1 (<0.1)	3 (0.1)
Pelvic fracture	0	0	0	1 (<0.1)
Periprosthetic fx	1 (<0.1)	0	1 (<0.1)	0
Pubis fracture	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Radius fracture	4 (0.1)	2 (0.1)	6 (0.1)	4 (0.1)
Rib fracture	7 (0.2)	10 (0.3)	17 (0.3)	8 (0.2)
Scapula fracture	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Skull fracture	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Spinal compression fx	1 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Spinal fracture	3 (0.1)	1 (<0.1)	4 (0.1)	0
Sternal fracture	4 (0.1)	0	4 (0.1)	0

Stress fracture	0	0	0	1 (<0.1)
Thoracic vertebral fx	2 (0.1)	0	2 (<0.1)	0
Tibia fracture	2 (0.1)	4 (0.1)	6 (0.1)	2 (0.1)
Ulna fracture	2 (0.1)	0	2 (<0.1)	0
Upper limb fracture	2 (0.1)	4 (0.1)	6 (0.1)	1 (<0.1)
Wrist fracture	7 (0.2)	3 (0.1)	10 (0.2)	4 (0.1)
All subjects with fracture	**76 (2.5)**	**70 (2.3)**	**146 (2.4)**	**57 (1.7)**
Source: 4-Month Safety Update, p. 58 (Table 29) and table, pp. 146-151				

To examine potential associations with fracture events in the DS4 dataset, the Applicant conducted a multivariate analysis of post-randomization low trauma fractures, applying the Andersen-Gill model. Statistically significant factors associated with an increased risk of low trauma fractures in this population include a prior history of fractures and older age. Canagliflozin treatment was not associated with an increase in low trauma fractures (hazard ratio of 1.26, 95% CI: 0.834 to 1.892, p=0.257) in this multivariate analysis:

Andersen-Gill model for the analysis of occurrences of post randomization low trauma fractures (DS4, ISS)

Variable	Coefficient	SE	Chi-square test	p-value	Hazard ratio*	HR 95% CI
Treatment group (All Cana=1, All Non-Cana=0)	0.228	0.209	1.190	0.275	1.256	0.834, 1.892
Age	0.035	0.012	9.096	0.003	1.036	1.012, 1.060
Gender (male=1, female=2)	0.278	0.541	0.264	0.607	1.320	0.457, 3.813
Baseline menopausal status (yes=1, no=0)	0.470	0.539	0.762	0.383	1.600	0.557, 4.599
Prior history of fractures (yes=1, no=0)	0.689	0.257	7.183	0.007	1.991	1.203, 3.295
* Hazard ratio > 1 indicates increased risk in subjects with larger values of the explanatory variable Source: ISS p. 2366						

PPARγ exposure: Of the 159 subjects with fractures reported in the ISS, only 3 were in subjects receiving a PPARγ as background therapy. These were: a 52 y/o female placebo subject with left foot and great toe fracture; a 62 y/o male Cana 100 mg subject with metacarpal fractures; and a 76 y/o male placebo subject with C-6 and C-7 fractures due to MVA.
Reviewer comment: *These are unlikely to be fragility-related fractures, thus it does not appear that PPARγ use had an effect on fractures in these studies.*

Gender:
Analysis by gender shows that women, who constituted 42% of phase 3 subjects, accounted for most of the upper extremity fractures, and most of the treatment imbalance

thereof. (see table) The mean age of the subjects with upper extremity fractures was 63 y/o for both men and women. The mean study day of the fracture was 234 days.

Phase 3 subject incidence of fractures post-randomization, by skeletal region and gender (DS4, 4-Month Safety Update)

	Cana 100 mg n (%)	Cana 300 mg n (%)	All Cana n (%)	All Non-Cana n (%)
Men, N	1803	1766	3569	1924
Total w/ fractures	33 (1.8)	35 (2.0)	68 (1.9)	27 (1.4)
Adjudicated pos.	28 (1.6)	31 (1.8)	59 (1.7)	26 (1.4)
Lower limb	13	13	26	17
Upper limb	7	13	20	7
Women, N	1289	1319	2608	1338
Total w/ fractures	43 (3.3)	35 (2.7)	78 (3.0)	30 (2.2)
Adjudicated pos.	40 (3.1)	30 (2.3)	70 (2.7)	27 (2.0)
Lower limb	12	12	24	12
Upper limb	21	14	35	10
Source: 4-Month Safety Update Table 32, p. 61				

The treatment imbalance in women was most notable in wrist fractures. The following table is derived from the ISS dataset therefore does not reflect either the adjudications or the 4 month safety update:

Phase 3 subject incidence of upper extremity fractures in women post-randomization (ISS)

	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total upper limb	**13**	**12**	**25**	**5**
Humerus fracture	3	6	9	2
Radius fracture	3	1	4	2
Ulna fracture	1	0	1	0
Wrist fracture	**5**	**3**	**8**	**0**
Upper limb fracture	1	2	3	1
Source: ISS dataset				

Of the upper extremity fractures in the ISS dataset, 25% occurred within 12 weeks of starting study medication and 42% within 26 weeks, and the disparity in fractures between treatment groups was apparent within the first 12 weeks, as noted above. The Applicant considered that these short time frames would be unlikely to reflect treatment-related changes in bone susceptibility to fracture (e.g. changes in BMD). Thus they investigated the possibility of other factors, in particular an increase in falls related to canagliflozin's potential for dehydration and/or volume depletion. There did appear to be increases in such symptoms as hypotension, orthostatic hypotension and postural dizziness associated with the larger (300 mg) Cana dose, especially during the first 30 days of treatment. However, the Applicant conducted a detailed review of narratives on all subjects with upper limb fractures, and did not find any to include reports of orthostatic hypotension, postural dizziness, lightheadedness, dizziness, presyncope or

syncope. Moreover, subjects with low trauma fractures did not display notable changes from baseline in hemoglobin, BUN, creatinine, systolic or diastolic blood pressure, and none were reported to have a hypoglycemic episode on the day of the fracture.

Renal Impairment
Fractures were assessed in the subset of phase 3 subjects (n=1087) with moderate renal impairment, defined as eGFR 30-59 mL/min/1.73 m^2. There were 21 fracture AEs in this group, including 17 which were positively-adjudicated, with a slight preponderance in the Cana 100 mg group:

Subject incidence of post-randomization fractures in subjects with moderate renal impairment, by skeletal region (Phase 3, 4-Month Safety Update)

	Cana 100 mg (N=339) n (%)	Cana 300 mg (N=365) n (%)	All Cana (N=704) n (%)	All Non-Cana (N=383) n (%)
Total with fracture AEs	9 (2.7)	6 (1.6)	15 (2.1)	6 (1.6)
Total positively adjudicated	9 (2.7)	4 (1.1)	13 (1.8)	4 (1.0)
Lower limb	1	2	3	2
Upper limb	3	2	5	1
Spine	3	0	3	1
Thoracic cage	1	1	2	0
Pelvis	1	0	1	0
Source: 4-Month Safety Update Table 33, p. 63				

Summary and Conclusions
Canagliflozin is an NME oral agent for treatment of Type 2 diabetes, which acts through inhibition of SGLT2 in the renal tubule. This drug and a related SGLT2 inhibitor, dapagliflozin, are associated with altered calcium metabolism and hyperostosis of trabecular bone in rats. However, these drugs did not show any significant changes in calcium metabolism in clinical studies. Canagliflozin appears to cause a small increase in serum phosphorus and magnesium levels, and possibly a slight decline in 1,25-OH-vitamin D levels. In the key phase 2 study, this drug also was associated with a slight increase in PTH levels at 3 weeks, however PTH returned to baseline at 6 and 12 weeks, and phase 3 subjects with moderate renal impairment experienced a slight decline in PTH relative to placebo.

Previously, clinical trials of dapagliflozin did not show any consistent changes in bone turnover markers or bone mineral density. In contrast, canagliflozin demonstrated, in a population of 716 older adults (age 55-80, mean 63 y/o, 55% male), placebo-corrected increases from baseline in serum CTX (a marker of bone resorption) of 17% and 25% for the 100 mg and 300 mg doses respectively at 26 weeks, which were statistically significant (Study DIA3010). Serum P1NP, a marker of bone formation, showed minimal increases in the Cana groups which were less than placebo, and not significant, in this study.

The mechanism of the apparent dose-dependent increase in bone resorption is unclear. There was a mean weight loss of 2.4 kg and 3.0 kg (for 100 mg and 300 mg doses respectively) at 26 weeks in this study. Weight loss, particularly in the absence of a concomitant increase in exercise or physical activity, is typically associated with increased bone resorption and CTX levels, and decreased BMD. However, dapagliflozin resulted in weight loss comparable to canagliflozin, presumably via the same mechanisms, without a significant effect on CTX or other bone markers.

A 17-25% increase in CTX might have been expected to result in significant declines in week 26 BMD, however observed BMD changes in study DIA3010 were small and inconsistent at lumbar spine, with small decreases at 1/3 radius, and small decreases at total hip (-0.4% and -0.5%) but small increases at femoral neck (+0.3% and +0.4%). Only the decreases at total hip reached statistical significance, and the Applicant is probably correct in their conclusion that the magnitude of the BMD changes is not sufficient to have clinical significance. The additional data anticipated from this study (DXA at weeks 52 and 104, QCT at week 52 in a subset) will be required before any definitive conclusions on the effect of Cana on bone density may be reached.

An analysis of clinical fractures in nearly 10,000 phase 3 Type 2 diabetics (mean age 60 y/o, 58% male) showed apparent canagliflozin-associated increases in overall fractures (2.5%, 2.3% and 1.7% for Cana 100 mg, Cana 300 mg and control respectively); overall positively-adjudicated fractures (2.2%, 2.0% and 1.6%); positively-adjudicated low-trauma fractures (1.6%, 1.6%, and 1.2%); overall upper extremity fractures (0.9%, 0.9% and 0.5%); and positively-adjudicated low-trauma upper extremity fractures (0.7%, 0.7% and 0.3%). The imbalance appears to be most pronounced in women with wrist fractures. There is also an imbalance in adjudicated low-trauma spine fractures (5, 1 and 0 for the three groups). These fracture results differ from those of the related drug dapagliflozin which was not associated with an overall increase in fractures. Conversely, studies of subjects with moderate renal impairment showed a dose-related increase in fractures with dapagliflozin, but not canagliflozin.

There are several factors to consider in interpreting these fracture results. The treatment group comparisons do not reach statistical significance, except for borderline-significance of the overall (prior to adjudication, and without regard to trauma) fractures at all sites combined. However, the phase 3 program was not specifically powered to rule out an increase in fractures, which are relatively infrequent even in a sample population of 10,000. Canagliflozin was associated with increased upper extremity fractures relative to control, however lower limb fractures display somewhat of the opposite trend, and there are no apparent dosage effects between 100 mg and 300 mg in any category of fractures. There are fewer phase 3 dropouts with Cana relative to control, thus somewhat greater mean observation time for detection of fractures. The Applicant notes that the treatment imbalance in low-trauma fractures is apparent within 12 weeks of treatment and that there is a dose related increase in events of postural dizziness and orthostatic hypotension, though it is unclear whether these help to explain the fracture findings.

In summary, clinical trials of canagliflozin demonstrate a modest dose dependent increase in bone resorption, which may contribute to bone fragility. There is also a potential increase in fractures, however the latter is apparent within 12-26 weeks of treatment, during which time frame there is no apparent decline in bone density sufficient to provide plausibility for this mechanism. The potential excess in fractures was essentially limited to the upper extremity, which would be highly unusual for a bone fragility issue. This suggests that falls may be a factor, though the information submitted is not sufficient to reach any conclusions about this. Further data on BMD and fractures will be forthcoming and will be needed to determine if there is a safety signal for fractures.

Labeling

The Applicant has not proposed any labeling content related to any of the bone-related data with the exception of the following statement in section 14.3 Studies in Special Populations/ Study in Older Patients, referring to week-26 DXA data from study DIA3010:

> *There were no meaningful changes in bone density in trabecular and cortical regions.*

DRUP Recommendations

1. The above-noted proposed labeling statement should be modified to: *There were no meaningful changes in bone density <u>through week 26</u>.* Specifying cortical and trabecular BMD is not warranted.
2. We do not believe that the fracture data warrant any labeling at this time. However, we would defer to DMEP regarding this issue. In any case, it will be important to re-evaluate the bone data at the conclusion of study DIA3010, when the additional DXA data (weeks 52 and 104) are available. Updated fracture data should also be re-evaluated at that time, including fractures through the conclusion of study DIA3010 and fractures reported up to that time in study DIA3008. This information should include narratives of all (cumulative) reported fracture events and the adjudication decisions made regarding each one. We recommend making these trials PMRs, to assure that the additional bone data are submitted in a timely manner. DRUP would like the opportunity to review the additional data.
3. Based on current data, it is acceptable to not include the bone marker data (CTX) in labeling, as there is no evidence that it has clinical significance. However, if updated fracture data, and/or additional DXA data (weeks 52 and 104) were to indicate a significant bone safety issue, the CTX information should be included in the added labeling.

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

/s/

STEPHEN R VOSS
12/04/2012

THERESA E KEHOE
12/05/2012

HYLTON V JOFFE
12/05/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 2, 2012

From: Aliza Thompson, MD, Medical Officer
Division of Cardiovascular and Renal Products

Through: Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products

To: Jena Weber, Regulatory Project Manager
Division of Metabolic and Endocrine Products

Subject: Consult to evaluate and comment on the renal safety findings associated with canagliflozin use in NDA 204042

Background

Canagliflozin is an inhibitor of sodium-glucose transporter 2 (SGLT2) and has been developed by the applicant to improve glycemic control in adults with type 2 diabetes mellitus (NDA submitted in May 2012). The SGLT2 transporter in the proximal renal tubule is thought to reabsorb the majority of glucose filtered by the renal glomerulus. SGLT2 inhibitors lower plasma glucose levels by decreasing renal glucose re-absorption. Although there are no approved agents in this class in the U.S., there are other SGLT2 inhibitors in various stages of development.

Because of their mechanism of action, intravascular volume depletion has been a concern with SGLT2 inhibitors. There has also been concern for potential adverse renal effects secondary to volume depletion. In the canagliflozin development program, an early and dose-dependent increase in serum creatinine and BUN levels was observed. Early and dose-dependent increases in creatinine were also reported in the development program of another SGLT2 inhibitor, dapaglifozin (see FDA Briefing Document for NDA 202293, Dapaglifloizin tablets, ACM July 19, 2011).

This consult from the Division of Metabolic and Endocrine Drug Products asks for comment from the Division of Cardiovascular and Renal Products on the renal safety findings in the canagliflozin development program, as well as their clinical significance.

Sources of data

In support of the proposed indication, the applicant conducted nine phase 3 trials in subjects with type 2 diabetes using the doses of canagliflozin proposed in labeling (100 mg and 300 mg). An overview of these trials is provided in the table below. Four of these trials had a placebo control and excluded subjects with an eGFR < ~50-60 mL/min/1.73 m^2. Two were active-controlled and also excluded subjects with an eGFR in the aforementioned range. In addition, three placebo-controlled trials were conducted/are underway in special populations as defined by age, renal impairment and cardiovascular risk. The trial conducted in subjects with moderate renal impairment (DIA3004) enrolled subjects with an eGFR ≥30 and <50 mL/min/1.73 m^2. The applicant's cardiovascular outcome study (DIA3008) allowed enrollment of subjects with an eGFR <30 mL/min/m^2. The trial conducted in older subjects excluded subjects with an eGFR <50 mL/min/m^2.

Table 1. Overview of Phase 3 studies in subjects with type 2 diabetes mellitus

Study / Population	Background Therapy	Design/Duration[a]	Number of Randomized Subjects	Study Treatment Groups
Phase 3 Placebo–controlled Studies				
DIA3005 (general T2DM)				
Main Study	Diet/exercise	Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=587 (excluding high glycemic cohort)	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
High Glycemic Cohort	Diet/exercise	26 weeks double-blind	N=91	1) Canagliflozin – 100 mg 2) Canagliflozin – 300 mg
DIA3002 (general T2DM)	Metformin and sulphonylurea	Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=469	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA3006[b] (general T2DM)	Metformin	Placebo- and active-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=1284	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg 4) Sitagliptin – 100 mg
DIA3012 (general T2DM)	Metformin and pioglitazone	Placebo-controlled 52 weeks double blind (26 weeks core/26 weeks extension period)	N=344	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
Phase 3 Active–controlled Studies				
DIA3009 (general T2DM)	Metformin	Active-controlled 104 weeks double blind (52 weeks core/52 weeks extension period)	N=1452	1) Canagliflozin – 100 mg 2) Canagliflozin – 300 mg 3) Glimepiride (titrated 1 mg up to a maximum[c] of 6 to 8mg)
DIA3015 (general T2DM)	Metformin and sulphonylurea	Active-controlled 52 weeks double blind	N=756	1) Canagliflozin – 300 mg 2) Sitagliptin – 100 mg

Table 1 Continued

Study / Population	Background Therapy	Design/Duration[a]	Number of Randomized Subjects	Study Treatment Groups
		Phase 3 Studies in Special Populations		
DIA3010 (T2DM / older [≥55 years] subjects)	Any diabetes therapy (diet or oral or parenteral AHA)	**Older Subjects (ie, ≥55 to ≤80 years of age) /Bone Density Evaluation** Placebo-controlled 104 weeks double blind (26 weeks core/78 weeks extension period)	N=716	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA 3004 (T2DM with moderate renal impairment population)	Any diabetes therapy (diet or oral or parenteral AHA)	**Study in Subjects with Moderate Renal Impairment** Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=272	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA3008[d] (T2DM with CV disease or at high risk for CV disease)	Any diabetes therapy (diet or oral or parenteral AHA) Substudies: On insulin (≥20 units/day On SU agent (defined doses)	**Cardiovascular Study – Including 2 Efficacy and Safety Sub-studies (Insulin; SU)** Placebo-controlled, double-blind Event-driven; estimated duration of 4 to 8 years Duration of efficacy substudies: 18 weeks	N=4330 (total)	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg

AHA= antihyperglycemic agent

[a] All studies were multicenter, parallel-group studies; all canagliflozin doses are once-daily

[b] Study DIA3006 was both placebo- and active controlled.

[c] The maximum dose allowed based on the approved country-specific label

[d] The six strata in DIA-3008 were defined as:

Stratum 1: insulin monotherapy ≥20 units per day, on stable doses at least 10 weeks before the run-in visit

Stratum 2: insulin ≥20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy

Stratum 3: insulin ≥20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit

Stratum 4: sulphonylurea monotherapy, on stable doses at least 10 weeks before the run-in visit

Stratum 5: PPARγ agonist (pioglitazone ≥30 mg/day or rosiglitazone ≥4 mg/day) plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other background AHA therapy, on stable doses at least 10 weeks before the run-in visit

Stratum 6: subjects not in one of the above AHA subgroups

Source: Summary of Clinical Safety, Table 2

The pooled datasets described below are referenced in this review. Results of some individual studies are also discussed.

- Placebo-controlled studies dataset (DS1)- includes data to week 26 from the four placebo-controlled phase 3 studies that excluded subjects with an eGFRs <~50-60 mL/min/1.73^2 (DIA3002, DAI3005, DIA3006 and DIA3012). The median age in this dataset is 57 and median baseline eGFR is 86 mL/min/1.73^2.
- Moderate renal impairment dataset (DS2)- includes data from subjects with a baseline eGFR ≥30 to < 60 mL/min/1.73m^2 (DIA3004 and a subset of subjects enrolled in DIA3005, DIA3008 and DIA3010; data up to the data cut-off date of September 15, 2011 for DIA3008 and up to week 26 for the other studies). The median age in this dataset is 67 and median baseline eGFR is 50 mL/min/1.73m^2; approximately one-third of subjects had an eGFR <45 mL/min/1.73m^2. Subjects in this dataset had a mean duration of exposure of 36 and 33 weeks in the canagliflozin and placebo arms, respectively.

Renal safety findings

In phase 1 studies, treatment with canagliflozin was associated with early increases in urine volume and serum creatinine and BUN levels, and decreases in blood pressure. In the phase 3 trials, an early and dose-dependent decrease in eGFR was also observed, which did not appear to worsen with continued therapy. As shown in the figures below, the magnitude of the initial drop in eGFR (relative to placebo) and its pattern/persistence over time, appeared to vary

somewhat, depending upon the population studied. Corresponding treatment-induced changes in BUN (i.e., an early increase and persistent elevation) were also seen.

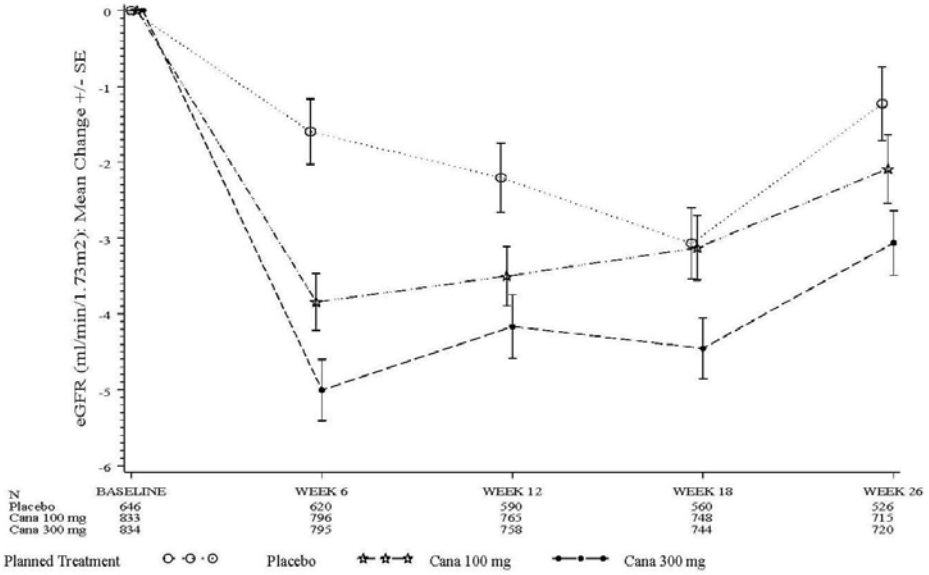


Figure 1. Mean Change (+/-SE) in eGFR from baseline in the placebo-controlled studies dataset
Source: ISS, Figure 18

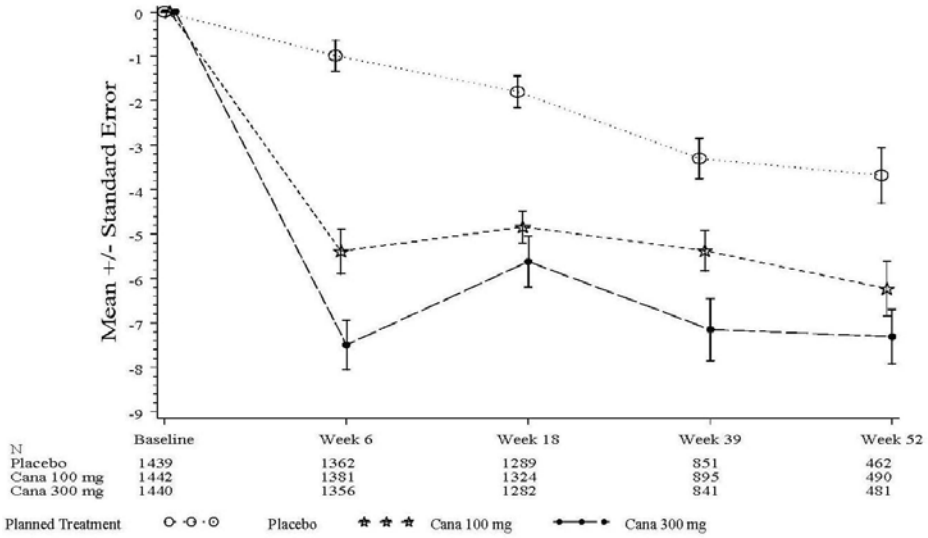


Figure 2. Mean Change (+/-SE) in eGFR from baseline in DIA3008
Source: ISS, Figure 20

With regard to the reversibility of treatment induced changes in eGFR, routine post-treatment laboratory assessments were not performed in the phase 3 diabetes studies.[1] However,

[1] In a phase 2 study in non-diabetic overweight/obese subjects (study OBE2001), laboratory values were obtained two weeks after therapy (50, 100 and 300 mg). However, when compared to placebo, no marked/clear change in eGFR from baseline to week 12 was seen on therapy in the treatment arms (mean change [SD] of 0.3 [13.6] on placebo, -1.0 [11.3] on 50 mg QD, -1.8 [14.6] on 100 mg QD and 0.8 [12.8] on 300 mg QD).

reductions in systolic and diastolic blood pressure were observed in phase 3 trials, providing support for a hemodynamically mediated drug effect on eGFR. Moreover, in studies where urine albumin/creatinine ratios were measured, there appeared to be a slight reduction from baseline in urine albumin to creatinine ratios in the canagliflozin as compared to the placebo arm (see appendix for both).

To further explore the potential clinical significance of canagliflozin's effect on eGFR, the applicant examined treatment effects on the incidence of more marked changes in eGFR (arbitrarily defined by the applicant as an eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline or a >50% reduction from baseline). In the applicant's analysis of the placebo-controlled trials dataset, the incidence of these events appeared to be similar in the 100 mg dose and placebo treatment arms, and greater in the 300 mg dose group. In contrast, in analyses of subjects with moderate renal impairment, the incidence of more marked changes in renal function appeared to be greater in both the 100 mg and 300 mg groups when compared to the placebo group. Consistent with analyses of mean effects, the Kaplan-Meir plot of time to first eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline showed an early separation of curves.

Table 2. Number of subjects with eGFR values below specified limits

	Placebo n (%)	Canagliflozin 100 mg n (%)	Canagliflozin 300 mg n (%)
Phase 3 Placebo-Controlled Studies Dataset			
	624	809	805
eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline	13 (2.1)	16 (2.0)	33 (4.1)
eGFR decrease >50% from baseline	1 (0.2)	0	1 (0.1)
Phase 3 Moderate Renal Impairment Dataset			
	367	332	352
eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline	18 (4.9)	31 (9.3)	43 (12.2)
eGFR decrease >50% from baseline	0	5 (1.5)	3 (0.9)

Sources: ISS Tables 133 and 134. Any post-baseline value; percentages calculated with the number of subjects per time interval as denominator.

The incidence of renal related adverse events and renal-related adverse events leading to discontinuation was also compared across treatment arms.[2] In the phase 3 placebo-controlled trials, the incidence of renal-related adverse events and renal-related adverse events leading to discontinuations was low, though appeared to be slightly greater in the canagliflozin 300 mg dose group compared to the placebo and 100 mg dose groups. In the moderate renal impairment dataset, the incidence of these events was higher than that seen in the placebo-

[2] No systematic approach appears to have been taken to ensure the capture of renal-related adverse events in the phase 3 trials. The applicant identified potential renal-related adverse events from the larger pool of investigator reported adverse events using the SMQ for acute renal failure adverse events and a broader list of "renal related adverse events" (this list included terms under the SMQ for acute renal failure and the terms blood creatinine increased and glomerular filtration decreased).

controlled studies dataset. The incidence was also greater in both the 100 mg and 300 mg dose groups, when compared to placebo.

Table 3. Number (%) of subjects with at least one adverse event of the following types

	Placebo n (%)	Canagliflozin 100 mg n (%)	Canagliflozin 300 mg n (%)
Phase 3 Placebo-Controlled Studies Dataset			
	646	833	834
Any selected renal-related adverse event	4 (0.6)	5 (0.6)	14 (1.7)
Any selected renal-related adverse event leading to discontinuation	1 (0.2)	3 (0.4)	7 (0.8)
Any selected renal-related adverse event related to study drug	3 (0.5)	2 (0.2)	8 (1.0)
Any selected renal-related serious adverse events	0	1 (0.1)	0
Phase 3 Moderate Renal Impairment Dataset			
	382	338	365
Any selected renal-related adverse event	14 (3.7)	30 (8.9)	34 (9.3)
Any selected renal-related adverse event leading to discontinuation	4 (1.0)	4 (1.2)	6 (1.6)
Any selected renal-related adverse event related to study drug	10 (2.6)	10 (3.0)	20 (5.5)
Any selected renal-related serious adverse events	5 (1.3)	4 (1.2)	5 (1.4)

Sources: ISS Tables 142 and 145. Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication

In addition to the aforementioned approaches to exploring canagliflozin's renal-related risks, the applicant established a Clinical Events Committee to adjudicate in a blinded fashion the potential causal relationship between events of particular interest and study drug. Criteria for CEC adjudication were as follows[3] :

- Sustained doubling of serum creatinine from the baseline value (or ≥50 % decrease in eGFR from baseline) that occurred while the subject was on study drug. The definition of "sustained" was a repeat value occurring ≥4 weeks after the initial finding and with the subject having remained on study drug.
- Doubling in baseline serum creatinine (or ≥50% decrease in baseline eGFR) at last recorded laboratory value. A "last" value is defined as either last available value in subjects who completed the study or discontinued early, or as the last value available at the time of study cut-off date in subjects who continued in the study (and may have had follow-up values on drug after study cut-off date).
- End stage renal disease (ESRD, new or worsening) or renal replacement (dialysis or transplant). The CEC Charter contains terms used to search the clinical and safety databases to identify potential ESRD and/or renal replacement cases to be adjudicated

[3] According the applicant, cases were identified by review of reported local laboratory values (e.g., during hospitalization) from the sponsor's Global Medical Safety database by searching for absolute values of serum creatinine ≥ 1.2 mg/dL and/or eGFR < 60 mL/min/1.73m^2. The serum creatinine and eGFR absolute values identified in the safety database search were then compared with baseline values to determine if the case met adjudication criteria.

As of the 4-Month Safety Update, a total of 43 cases were identified that met the adjudication criteria and had adjudication results (15 in the control arm, 12 in the canagliflozin 100 mg arm and 16 in the canagliflozin 300 mg arm). The first table shows the criteria that the cases met by treatment arm; the second table shows the adjudication results for causation. The number of events is small and no clear differences are seen among the treatment arms.

Table 4. Summary of cases sent for Renal Clinical Events Committee Adjudication

CEC Criteria	All Non-Cana n/N (%)	Cana 100 mg n/N (%)	Cana 300 mg n/N (%)	All Cana n/N (%)
Any[a]	15/3640(0.41)	12/3092(0.39)	16/3462(0.46)	28/6554(0.43)
Sustained[b] elevation in serum creatinine	0	0	0	0
Sustained[b] decrease in eGFR	4/3640(0.11)	0	2/3462(0.06)	2/6554(0.03)
Last value elevation in serum creatinine	4/3640(0.11)	3/3092(0.10)	5/3462(0.14)	8/6554(0.12)
Last value decrease in eGFR	10/3640(0.27)	6/3092(0.19)	11/3462(0.32)	17/6554(0.26)
ESRD or renal replacement (dialysis or transplant[c])	1/3640(0.03)	4/3092(0.13)	1/3462(0.03)	5/6554(0.08)

Note: N is the total number of subjects from Phase 3 studies: DIA3002, DIA3004, DIA3005 (main study), DIA3006, DIA3008, DIA3009, DIA3010, DIA3012 and DIA3015, events for the renal adjudication in these studies up to July 1 2012 were included.

[a]Any refers to any of the CEC adjudication criteria
Source: 4-Month Safety Update Report, Table 27

Table 5. Summary of CEC Causality assessment for cases sent for CEC Adjudication

CEC Criteria Causality	All Non-Cana n/N (%)	Cana 100 mg n/N (%)	Cana 300 mg n/N (%)	All Cana n/N (%)
Any[a]				
Number of Cases[b]	15	12	16	28
Very Likely	0	0	0	0
Probable	1/3640(0.03)	1/3092(0.03)	2/3462(0.06)	3/6554(0.05)
Possible	8/3640(0.22)	4/3092(0.13)	8/3462(0.23)	12/6554(0.18)
Doubtful	3/3640(0.08)	2/3092(0.06)	4/3462(0.12)	6/6554(0.09)
Not Related	3/3640(0.08)	5/3092(0.16)	2/3462(0.06)	7/6554(0.11)

Note: N is the total number of subjects from Phase 3 studies: DIA3002, DIA3004, DIA3005 (main study), DIA3006, DIA3008, DIA3009, DIA3010, DIA3012 and DIA3015, events for the renal adjudication in these studies up to July 1 2012 were included.

[a]Any refers to any of the CEC adjudication criteria
Source: 4-Month Safety Update Report,Table 28

Susceptible populations

As indicated in prior analyses, compared to subjects with relatively well-preserved renal function, subjects with moderate renal impairment appear to be at greater absolute risk of developing more marked changes in renal function on canagliflozin. Additional subgroup analyses were also conducted in an attempt to identify factors that might increase the risk of clinically significant changes in renal function on canagliflozin. As shown in the table below, in univariate analyses, factors associated with the most notable increase in risk included a GFR < 60, age ≥ 65, use of diuretics, and use of ACEI/ARBs (particularly in combination with a diuretic).

Table 6. Subgroup analysis of number of subjects with any post-baseline eGFR value mL/min/1.73m^2 and > 30% decrease (Broad dataset)

	n (%) in population[b]	Incidence[a] Cana 100 mg % (n/N)	Cana 300 mg % (n/N)	All Cana % (n/N)	All Non-Cana % (n/N)
eGFR (mL/min/1.73m^2)	N=9439				
<60	1223 (13.0%)	8.4% (32/382)	10.9% (44/405)	9.7% (76/787)	4.1% (18/436)
60 to <90	5154 (54.6%)	3.6% (61/1686)	4.9% (83/1680)	4.3% (144/3366)	3.3% (59/1788)
≥90	3055 (32.4%)	3.2% (33/1021)	6.1% (61/999)	4.7% (94/2020)	4.5% (47/1035)
Sex	N=9439				
Male	5493 (58.2%)	3.3% (59/1803)	5.9% (104/1766)	4.6% (163/3569)	3.6% (69/1924)
Female	3946 (41.8%)	5.2% (67/1289)	6.4% (84/1319)	5.8% (151/2608)	4.1% (55/1338)
Age (years)	N=9439				
<65	6509 (69.0%)	3.8% (80/2110)	5.4% (115/2114)	4.6% (195/4224)	3.9% (89/2285)
≥65	2930 (31.0%)	4.7% (46/982)	7.5% (73/971)	6.1% (119/1953)	3.6% (35/977)
Baseline HbA1c (%)	N=9434				
≤7.9	4894 (51.9%)	4.3% (67/1563)	6.0% (97/1607)	5.2% (164/3170)	3.6% (62/1724)
>7.9	4540 (48.1%)	3.9% (59/1527)	6.2% (91/1477)	5.0% (150/3004)	4.0% (62/1536)
Use of ACE/ARB	N=9439				
No	2961 (31.4%)	1.9% (18/970)	3.5% (34/969)	2.7% (52/1939)	2.9% (30/1022)
Yes	6478 (68.6%)	5.1% (108/2122)	7.3% (154/2116)	6.2% (262/4238)	4.2% (94/2240)
Use of Diuretics[c]	N=9439				
No	6118 (64.8%)	2.6% (53/2016)	4.0% (81/2009)	3.3% (134/4025)	3.2% (68/2093)
Yes	3321 (35.2%)	6.8% (73/1076)	9.9% (107/1076)	8.4% (180/2152)	4.8% (56/1169)
Use of Loop Diuretics	N=9439				
No	8717 (92.4%)	3.4% (98/2876)	5.4% (154/2835)	4.4% (252/5711)	3.5% (104/3006)
Yes	722 (7.6%)	13.0% (28/216)	13.6% (34/250)	13.3% (62/466)	7.8% (20/256)
Use of ACE/ARB and/or Diuretics	N=9439				
Not using ACE,/ARB, or diuretics	2611 (27.7%)	1.5% (13/871)	2.5% (21/850)	2.0% (34/1721)	2.7% (24/890)
ACE/ARB only	3507 (37.2%)	3.5% (40/1145)	5.2% (60/1159)	4.3% (100/2304)	3.7% (44/1203)
Diuretics only	350 (3.7%)	5.1% (5/99)	10.9% (13/119)	8.3% (18/218)	4.5% (6/132)
ACE/ARB and diuretics	2971 (31.5%)	7.0% (68/977)	9.8% (94/957)	8.4% (162/1934)	4.8% (50/1037)
Duration of Diabetes (years)	N=9439				
<10	4705 (49.8%)	3.6% (56/1536)	5.2% (78/1502)	4.4% (134/3038)	3.3% (55/1667)
≥10	4734 (51.2%)	4.5% (70/1556)	6.9% (110/1583)	5.7% (180/3139)	4.3% (69/1595)
Diabetes Complications	N=9439				
No	6312 (66.9%)	3.1% (65/2066)	4.7% (96/2032)	3.9% (161/4098)	3.3% (72/2214)
Yes	3127 (33.1%)	5.9% (61/1026)	8.7% (92/1053)	7.4% (153/2079)	5.0% (52/1048)

[a] Incidence of eGFR values outside pre-defined limit (<80 mL/min/1.73m^2 and >30% decrease from baseline).
[b] Number of subjects in the total population with the baseline characteristic.
[c] Includes both loop and non-loop diuretics.

Source: ISS, Table 138

Consult Questions

The consult requests comment from DCRP on the following:
1. Please comment on whether the data support the theory that observed changes in renal function were due to hypovolemia alone and fully reversible.

The data as a whole suggest the observed changes in renal function are secondary to volume depletion. Although one would expect reversibility following drug discontinuation and correction of volume depletion, the applicant has not provided data that speak to the long term renal consequences of extended exposure to the drug in the proposed population (see also response to question 2).

2. Please comment on the potential clinical impact these changes in renal function may have in a population of patients with diabetes with normal renal function and in a population of patients with diabetes and moderate renal impairment.

The long term renal consequences of canagliflozin's effect on eGFR are unknown. Given the available data, including the experience with other drugs that cause volume depletion, it seems prudent to assume that the volume depletion and corresponding reduction in eGFR caused by canagliflozin places patients at increased risk for clinically significant episodes of acute kidney injury (AKI) and that larger treatment effects on eGFR will translate into greater risk.

The analyses conducted by the applicant show a relatively low absolute incidence of more marked changes in eGFR on canagliflozin in subjects with normal and "near normal" levels of renal function. Thus, the incidence of clinically important adverse renal events may be low in patients with diabetes and normal renal function (assuming other similar characteristics to the study population). However, to get a better understanding of the nature of the treatment effect on eGFR in this population (and also other populations), you might want to consider comparing the distribution of the change from baseline in eGFR across treatment arms.

The amount of safety data in subjects with diabetes and moderate renal impairment is limited (particularly in subjects with an eGFR< 45 mL/min/1.73m^2) and what data exist suggest a high absolute risk of potentially clinically meaningful episodes of AKI at both doses and, in particular, at the high dose. This risk may be related to the presence of underlying renal disease, age, concomitant therapies commonly used in this population (such as diuretics), or a combination of these and possibly other factors. In addition, this risk may be magnified in the postmarketing setting when canagliflozin is used outside the carefully monitored setting of a clinical trial and in a less selected population. Given these issues, we think considerable uncertainty remains regarding renal safety in patients with diabetes and moderate renal impairment.

3. Please comment on whether differences in changes in renal function observed between the lower and higher dose of canagliflozin (i.e., 100 mg and 300 mg) supports the notion that the 100 mg dose is safer from a renal standpoint in subjects with moderate renal impairment.

Considering the relatively high incidence of >30% reductions from baseline in eGFR in patients with moderate renal impairment and the higher incidence of these reductions at the 300 mg as compared to the 100 mg dose, it is reasonable to think that the 100 mg dose might be safer from a renal standpoint in patients with diabetes and moderate renal impairment. (See also response to Question 2).

4. Please provide comments on the significance of the observed imbalance in adjudicated renal adverse events.

Based on the 4-Month Safety Update, there does not appear to be an imbalance in adjudicated events. The small number of events in each of the treatment arms is not unexpected given the population that was studied as well as the relatively short duration of many of these studies. The results indicate that in the population that was studied and over the time span of these studies, canagliflozin did not cause a marked or obvious increase in the rate of these events.

5. If it is not possible to address some of the comments above from the data in the NDA please comment on the type of study (ies) that would be needed to resolve these issues.

The ongoing study in patients with moderate renal impairment may provide further insight into safety in this population, though the trial may not be of sufficient duration to inform our understanding of the drug's long/longer-term effects on renal function. Given its longer duration, the applicant's cardiovascular outcome trial is likely to provide more insight into long term treatment effects on renal function. In both of these studies, it will be important to obtain creatinine measurements post treatment and at a time when any effects on volume status are likely to be resolved.

Appendix

Table 7. Mean change from baseline in blood pressure*

	Phase 3 Placebo Controlled Trials	Study 3004	Study 3008
Systolic Blood Pressure			
Placebo	-0.1 (11.8)	0.2 (14.8)	-1.6 (14.2)
Canagliflozin 100 mg	-3.9 (12.1)	-5.0 (14.4)	-4.3 (14.5)
Canagliflozin 300 mg	-5.3 (12.3)	-5.9 (12.6)	-6.3 (14.4)
Diastolic Blood Pressure			
Placebo	-0.3 (7.7)	-0.6 (7.3)	-1.1 (9.1)
Canagliflozin 100 mg	-2.1 (7.8)	-1.0 (8.3)	-2.4 (8.4)
Canagliflozin 300 mg	-2.5 (7.9)	-3.7 (7.3)	-3.4 (9.1)

Sources: CSR for 3004, Table 48; CSR for 3008, Table 32
*to Week 26 in 3004 and ISS Phase 3 Placebo-Controlled Studies Pooled and to Week 52 in 3008

Table 8. Urine albumin/creatinine ratio (g/mol): mean and median change from baseline to endpoint-within 2 days after the last dose of study drug

Lab Test Panel: First Morning Void				
DIA3004- Week 26	Placebo	CANA 100 mg	CANA 300 mg	CANA Total
N	63	61	62	123
Mean baseline	29.14	28.93	25.06	26.98
Mean change (SD)	-1.43 (39.241)	-13.42 (38.753)	-9.44 (38.877)	-11.42 (38.708)
Median change	-0.07	-0.85	-0.47	-0.49
DIA3005 – Week 26	Placebo	CANA 100 mg	CANA 300 mg	CANA Total
N	149	158	154	312
Mean baseline	2.39	2.35	2.70	2.52
Mean change (SD)	1.10 (13.975)	-0.65 (6.138)	-0.38 (6.723)	-0.52 (6.425)
Median change	0.05	0.01	-0.05	-0.02
DIA3008 – Week 52	Placebo	CANA 100 mg	CANA 300 mg	CANA Total
N	432	465	445	910
Mean baseline	11.50	7.04	8.99	7.99
Mean change (SD)	1.22 (23.734)	-0.64 (20.754)	-3.19 (18.802)	-1.89 (19.854)
Median change	0.09	-0.04	-0.11	-0.07
DIA3009 – Week 52	Glimepiride	CANA 100 mg	CANA 300 mg	CANA Total
N	369	378	362	740
Mean baseline	3.70	2.60	4.27	3.42
Mean change (SD)	0.79 (15.603)	-0.15 (4.843)	-1.22 (8.276)	-0.67 (6.761)
Median change	0.00	-0.01	-0.04	-0.02

Key: Cana=canagliflozin, N=total number of subjects; SD=standard deviation
Note: For each measurement, only those subjects who had both baseline and post baseline measurements were included.

Source: ISS, Table 139

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/s/

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12/02/2012

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12/02/2012