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*APPLICATION NUMBER:*

**204353Orig1s000**

**MEDICAL REVIEW(S)**

## Class 2 Re-submission Memorandum

<b>Date</b>	(electronic stamp)
<b>From</b>	Jean-Marc Guettier, MD
<b>Subject</b>	Division Director Memorandum for Regulatory Action
<b>NDA/BLA #</b>	204353
<b>Supplement #</b>	
<b>Applicant Name</b>	Janssen Research and Development, LLC
<b>Date of Submission</b>	February 10 <sup>th</sup> 2014
<b>PDUFA Goal Date</b>	August 8 <sup>th</sup> 2014
<b>Proprietary Name / Established (USAN) Name</b>	Invokamet (canagliflozin/metformin HCL)
<b>Dosage Forms / Strength</b>	Tablets Canagliflozin 50 mg/metformin 500 mg Canagliflozin 50 mg/ metformin 1000 mg Canagliflozin 150 mg/metformin 500 mg Canagliflozin 150 mg/metformin 1000 mg
<b>Proposed Indication(s)</b>	As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets
<b>Action/Recommended Action for NME:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	<b>Names of discipline reviewers</b>
Medical Officer	Kwon Hyon, PharmD
Office of Clinical Pharmacology	Anshu Marathe, PhD

On February 10<sup>th</sup>, 2014 Janssen Research and Development, LLC submitted a Class 2 resubmission of the new drug application for Invokamet under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act that references NDA 204042 for Invokana (canagliflozin) and NDA 20357 for immediate release metformin (metformin hydrochloride). Invokamet is a fixed dose combination (FDC) of canagliflozin and metformin hydrochloride. The resubmission is a complete response to the Complete Response Letter issued by the Agency on December 11<sup>th</sup>, 2013.

The application received a complete response due to clinical pharmacology deficiencies and the reasons are summarized in detail in a previous memorandum<sup>1</sup>. Briefly, the applicant relied on efficacy and safety data in NDA 204042 for Invokana to inform efficacy and safety of the FDC product (Invokamet). The canagliflozin administration schedule differs between Invokana and Invokamet, in the former canagliflozin is administered once daily and in the latter twice daily. To demonstrate that differences in canagliflozin administration schedules between the two products did not impact efficacy and safety, the applicant had compared canagliflozin steady state plasma concentration and urinary glucose excretion (UGE) between canagliflozin administered once daily (100 mg QD) and canagliflozin administered twice daily (50 mg BID) in a clinical pharmacology study. While these data suggested comparable pharmacodynamics based on urinary glucose excretion, the applicant had not adequately characterized the relationship between steady state canagliflozin plasma levels and HbA1c response (i.e., the actual measure of efficacy). Absent these bridging data, the Agency could not rely on efficacy and safety data from NDA 204042 to support approval of the fixed dose combination product.

In this submission, the applicant provides new clinical pharmacology data to bridge the two canagliflozin dosing regimens. The applicant, following advice received from the pharmacometric team within the Office of Clinical Pharmacology on December 19<sup>th</sup> 2013<sup>2</sup>, designed a strategy to establish a robust relationship between steady state canagliflozin plasma levels and HbA1c response. Once a robust understanding of the steady state canagliflozin exposure to HbA1c response relationship was established, the applicant compared the predicted HbA1c response time-course between a once and twice daily canagliflozin dosing regimen. Dr. Marathe has summarized the strategy and has reviewed the results obtained from these analyses in details in her memorandum<sup>3</sup>. She concludes that the applicant has demonstrated that HbA1c change from baseline is similar between once and twice daily canagliflozin dosing and that numerical differences between the two dosing regimens would not be considered clinically meaningful. In her review she quantifies the differences as follows: “the difference up to week 26 was at most 0.03% between the 50 mg BID and 100 mg QD regimens and 0.02% between the 150 mg BID and 300 mg QD regimens, with BID regimen showing slightly greater reduction in HbA1c”. The Office of Clinical

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<sup>1</sup> Refer to my memorandum in DARRTS dated December 10<sup>th</sup>, 2013

<sup>2</sup> Refer to meeting minutes in DARRTS dated January 15<sup>th</sup>, 2014

<sup>3</sup> Refer to Dr. Marathe’s memorandum in DARRTS July 20<sup>th</sup>, 2014

Pharmacology recommends approval of the application and states that the new data adequately address the deficiencies in the complete response letter and demonstrate through exposure-response analyses that differences in canagliflozin dosing regimens between Invokana and Invokamet would have little to no impact on HbA1c response.

The submission contained no new efficacy data. The applicant had shown in NDA 204042 and in trial **DIA2003** included in this application that canagliflozin added to background metformin improves glycemic control in patients with type 2 diabetes not adequately controlled on optimal doses of background metformin (summarized in my previous memorandum). The new and previously reviewed clinical pharmacology data (summarized in my previous memorandum) in aggregate have demonstrated that HbA1c response is similar whether canagliflozin and metformin are dosed as separate tablets or as an FDC product. In totality, these data support the stated claim.

Drs. Kwon and Yanoff have reviewed safety data accumulated since the last review cycle and have not identified a product safety concern that would alter the established benefit risk profile for canagliflozin used alone or in combination with metformin (refer to their reviews for full details). No changes to canagliflozin product labeling are recommended.

I agree with the review team and recommend approval of the application pending final agreement on labeling. At the end of phase 2 meeting on August 30<sup>th</sup>, 2010 and in the December 11<sup>th</sup>, 2013 Complete Response Letter the applicant was told that the two canagliflozin dosing regimens could be bridged using clinical pharmacology data provided that a robust understanding of the canagliflozin exposure to HbA1c response was established. With the data submitted in this resubmission the applicant establishes a robust canagliflozin exposure to HbA1c response and demonstrates that differences in canagliflozin dosing regimens between Invokana and Invokamet would have little to no impact on HbA1c response. The efficacy and safety of canagliflozin co-administered with metformin was established in NDA 204042. The data in NDA 204353 demonstrate that efficacy and safety is similar when canagliflozin and metformin are administered either as two tablets or as part of the FDC Invokamet product.

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/s/  
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JEAN-MARC P GUETTIER  
08/07/2014

## CLINICAL REVIEW

Application Type 505(b)(2)  
Application Number(s) 204535  
Priority or Standard Standard

Submit Date(s) February 10, 2014  
Received Date(s) February 10, 2014  
PDUFA Goal Date August 10, 2014  
Division / Office DMEP/ODE 2

Reviewer Name(s) Hyon J Kwon, PharmD, MPH  
Review Completion Date July 23, 2014

Established Name Canagliflozin/metformin HCL  
(Proposed) Trade Name Invokamet  
Therapeutic Class SGLT2 inhibitor and biguanide  
Applicant Janssen Research and Development, LLC

Formulation(s) Canagliflozin/metformin HCL IR FDC tablets at doses of 50/500, 50/1000, 150/500, and 150/1000 mg  
Dosing Regimen Twice daily  
Indication(s) As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets  
Intended Population(s) Type 2 diabetes mellitus

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

I recommend approval of the canagliflozin/metformin immediate release fixed dose combination for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

### **1.2 Risk Benefit Assessment**

This NDA was initially submitted on December 21, 2012 and received a Complete Response Letter (CRL) on December 12, 2013 because the clinical and clinical pharmacology data submitted to support approval were insufficient to bridge the once daily (QD) and twice daily (BID) dosing of canagliflozin. See section 2.5 of this review for further discussions regarding this issue.

In response to our CRL, the applicant resubmitted this NDA with a modeling and simulation data to bridge the efficacy of QD and BID dosing of canagliflozin. The Office of Clinical Pharmacology reviewed these data and has concluded that the data adequately demonstrate that the HbA1c change from baseline for QD and BID dosing regimens for canagliflozin are fairly similar and recommended approval.

This resubmission in response to our CRL did not contain any new clinical efficacy data, and my review of safety update did not show any new significant safety finding that is of concern. Therefore, the overall risk/benefit assessment of the combination of canagliflozin and metformin immediate release supports approval of this NDA.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No new safety concerns were identified that prompt the need for Risk Evaluation and Mitigation Strategies with canagliflozin/metformin IR FDC.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

Pediatric swallowability study: The required pediatric assessments under the Pediatric Research Equity Act (PREA) for canagliflozin/metformin IR FDC can be met by fulfilling

the required PREA studies under canagliflozin NDA, with the addition of a swallowability study with the FDC tablet as follows:

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

## **2 Introduction and Regulatory Background**

This is an NDA resubmission in response to FDA's Complete Response Letter dated December 11, 2013.

### **2.1 Product Information**

This is a 505(b)(2) NDA for approval of canagliflozin as fixed dose combination (FDC) with metformin HCL immediate release (IR), as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets. The reference listed drugs are canagliflozin (NDA 204-042) and the Glucophage (NDA 020-357).

Canagliflozin is an orally active, competitive, reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2), and metformin is an oral biguanide. The applicant proposes to market 50/500 mg, 50/1000 mg, 150/500 mg, 150/1000 mg of canagliflozin/metformin FDC, to be given twice daily (BID) with meals. It should be noted that canagliflozin is recommended to be taken before the first meal of the day, at a once daily (QD) dose of 100 mg and 300 mg. The posology of the proposed FDC is as BID administration because of metformin IR component which is given BID, and also with meals because metformin is recommended to be taken with meals to reduce the gastrointestinal side effects.

### **2.2 Tables of Currently Available Treatments for Proposed Indications**

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and the following drug therapies, either alone or in combination:

- Biguanides: metformin (e.g., Glucophage)
- Sulfonylureas: glyburide (Micronase), glipizide (Glucotrol), glimepiride (Amaryl), chlorpropamide (Diabinese), tolazamide (Tolinase)
- Insulin
- GLP-1 agonist: exenatide (Byetta), liraglutide (Victoza)

- Thiazolidinediones (TZDs): rosiglitazone (Avandia), pioglitazone (Actos)
- Dipeptidyl peptidase 4 (DPP-4) inhibitor: sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina)
- Meglitinides: repaglinide (Prandin), nateglinide (Starlix)
- $\alpha$ -Glucosidase inhibitor: acarbose (Precose), miglitol (Glyset)
- Pramlintide (Symlin)
- Dopamine agonist: bromocriptine mesylate (Cycloset)
- Bile acid sequestrants: colestevlam (WelChol)
- Various fixed dose combinations of oral therapies (e.g., Janumet, ActoPlus Met, Kombiglyze XR, Oseni, Kazano)

### **2.3 Availability of Proposed Active Ingredient in the United States**

Canagliflozin (NDA 204-402) and metformin (Glucophage, NDA 020-357) have been approved for the treatment of T2DM in the US since March 29, 2013 and March 3, 1995, respectively.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Labeled safety concerns with canagliflozin include the following:

- Contraindicated in patients with severe renal impairment (estimated GFR <30 mL/min/1.73m<sup>2</sup>), end-stage-renal disease, or on dialysis;
- Hypotension: the risk is increased in patients with renal impairment, elderly, low systolic blood pressure, or if on diuretics, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB);
- Impairment in renal function;
- Hyperkalemia: the risk is increased in patients with moderate renal impairment taking drugs that interfere with potassium excretion or ACEI or ARB;
- Hypoglycemia with concomitant use of insulin or insulin secretagogue;
- Genital mycotic infections;
- Hypersensitivity reaction;
- Increased LDL-C;
- Urinary tract infections.

Labeled safety concerns with metformin include the following:

- Lactic acidosis: the risk increases with sepsis, dehydration, excessive alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure;
- Contraindicated in patients with renal impairment (e.g., serum creatinine  $\geq$ 1.5 mg/dL for males,  $\geq$ 1.4 mg/dL for females, or abnormal creatinine clearance);
- Potential for acute alteration of renal function when undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures requiring restricted intake of food and fluids;

- Decrease in Vitamin B12 levels;
- Hypersensitivity;
- Hypoglycemia, in elderly and debilitated patients when calorie intake is deficient, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin).

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

See the Clinical Review dated November 1, 2013 of initial NDA submission for details of presubmission activity related to this NDA. See section 2.6 of both Clinical Review dated November 1, 2013 and this review for all regulatory activity that occurred during and after initial NDA submission.

On December 21, 2012, NDA 204-353 was submitted for canagliflozin/metformin IR FDC for the treatment of type 2 diabetes mellitus, to be administered twice daily. The critical issue for this NDA was bridging efficacy findings between once daily (QD) and twice daily (BID) dosing of canagliflozin, because canagliflozin was dosed QD in the single agent canagliflozin clinical program (NDA 204-042) and the total daily dose of canagliflozin is to be administered BID with this FDC due to metformin IR posology. The clinical and clinical pharmacology data submitted by the applicant appeared to be insufficient to bridge the efficacy, and we discussed our concerns related to bridging issue during Mid-Cycle meeting (see Mid-Cycle Communication Letter issued on June 6, 2013) as well as at Late-Cycle meeting on September 12, 2013 with the applicant (see Late-Cycle Meeting Minutes finalized September 26, 2013). Furthermore, we met with the applicant to discuss their modeling plan on December 19, 2013, and provided advice on the applicant's modeling strategy. See Clinical Pharmacology review which should detail all the communications related to our advice on modeling strategy.

On December 12, 2013, we issued a Complete Response Letter (CRL) because the clinical and clinical pharmacology data submitted to support approval were insufficient to bridge QD and BID dosing of canagliflozin. See CLR dated December 11, 2013, Clinical Review dated November 1, 2013, Clinical Pharmacology Review dated November 15, 2013, and Cross-Discipline Team Leader Review dated December 10, 2013 for details.

In the CRL, we indicated that the applicant can either submit the results of a robust modeling and simulation strategy to bridge the efficacy of once-daily to twice-daily dosing of canagliflozin, or conduct a head to head clinical trial comparing the efficacy of once-daily and twice-daily dosing of canagliflozin with sufficient duration (i.e., 12-16 weeks).

In the CRL, we requested a safety update per 21 CFR 314.50(d)(5)(vi)(b), which should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

See Memo dated January 10, 2014 for my review of applicant's safety update proposal for NDA resubmission.

## **2.6 Other Relevant Background Information**

None.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The quality of submission was acceptable for clinical data.

### **3.2 Compliance with Good Clinical Practices**

All the completed clinical trials new in this resubmission (i.e., (b) (4) DIA3014) were conducted in accordance with Good Clinical Practices by the applicant.

### **3.3 Financial Disclosures**

No financial disclosures were submitted with this resubmission because these were submitted and reviewed with the original NDA submission.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

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

No new data submitted. See CMC reviews by Dr. Markofsky dated October 28, 2013 and Dr. Eradiri dated July 16, 2013 completed during the initial NDA submission. Drs. Markofsky and Eradiri recommended approval of this NDA.

### **4.2 Clinical Microbiology**

Not applicable.

### 4.3 Preclinical Pharmacology/Toxicology

The applicant submitted 3 new nonclinical studies completed since the 4MSU: FK10426, FK10427, and TOX10433. No significant safety issues were seen in these studies. Please see Dr. Fred Alavi's review dated June 10, 2014 for review of new nonclinical studies. Dr. Alavi recommended approval of this NDA.

### 4.4 Clinical Pharmacology

Please see the review from the Office of Clinical Pharmacology (OCP) written by Drs. Anshu Marathe, Ritesh Jain, Lokesh Jain, and Nitin Mehrotra. The reviewers from the Office of Clinical Pharmacology recommended approval of this NDA as the sponsor has adequately addressed the deficiency in the CRL and demonstrated similar efficacy between the QD and BID dosing regimens through exposure-response analysis. See the OCP review dated July 20, 2014 for full details.

## 5 Sources of Clinical Data

Clinical data summarized in this resubmission was previously included in the original submission of the canagliflozin/metformin IR FDC NDA, except for safety update from newly initiated (blinded) or completed clinical trials since the 4-Month Safety Update (4MSU) under the original submission (which had a cut-off date of December 31, 2012).

### 5.1 Tables of Studies/Clinical Trials

Table 1 summarizes all Phase 2 and 3 trials supporting the canagliflozin/metformin IR FDC, modified from my Clinical Review dated November 1, 2013. No new efficacy data was submitted in this resubmission. See section 5.3 for brief discussion of new clinical trials that were submitted as part of the safety update.

**Table 1: Phase 2 and 3 Trials supporting the Canagliflozin/Metformin IR FDC**

Trial	Trial Design	Trial Population	Treatment Arms: # of Subjects Randomized	Duration
<b>Trials supporting Efficacy and Safety</b>				
<b>Phase 2 Trials</b>				
<b>DIA2001</b> Add-on to Metformin	Randomized, double-blind, placebo and active-controlled, double-dummy, parallel group, dose-ranging trial	HbA1c 7 to 10.5% inclusive	Cana 50 mg QD: 64 Cana 100 mg QD: 64 Cana 200 mg QD: 65 Cana 300 mg QD: 64 Cana 300 mg BID: 64 Sitagliptin 100 mg QD: 65 Placebo QD: 65	12 weeks
<b>DIA2003</b> Add-on to Metformin IR	Randomized, double-blind, placebo-controlled, parallel group, 18-week trial	HbA1c 7 to 10.5% inclusive	Cana 50 mg BID: 93 Cana 150 mg BID: 93 Placebo BID: 93	18 weeks

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Phase 3 Trials				
<b>DIA3006<sup>a</sup></b> Add-on to Metformin	Randomized, double-blind, placebo- and active-controlled, parallel group	T2DM subjects on metformin; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 368 Cana 300 mg: 367 Sitagliptin 100 mg: 366 Placebo: 183	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
<b>DIA3009</b> Add-on to Metformin	Randomized, double-blind, active-controlled, parallel group	T2DM subjects on metformin; HbA1c 7 to 9.5% inclusive	Cana 100 mg: 483 Cana 300 mg: 485 Glimepiride: 482	104 weeks (52-week active-controlled, core double-blind period plus a 52-week active-controlled, extension double-blind period )
<b>DIA3002</b> Add-on to Metformin + SU	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 157 Cana 300 mg: 156 Placebo: 156	52 weeks (26-week placebo-controlled, core double-blind period plus a 26-week placebo-controlled, extension double-blind period )
<b>DIA3012<sup>a</sup></b> Add-on to Metformin + Pioglitazone	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects on metformin + pioglitazone therapy; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 113 Cana 300 mg: 114 Placebo: 115	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
<b>DIA3015</b> Add-on to Metformin + SU	Randomized, double-blind, active-controlled, parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10.5% inclusive	Cana 300 mg: 377 Sitagliptin 100 mg: 378	52 weeks
<b>DIA3008</b> Insulin Substudy (Population 3) Add-on to insulin + metformin	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects on insulin $\geq$ 30 units/day + metformin $\geq$ 2000 mg/day; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 139 Cana 300 mg: 148 Placebo: 145	18 weeks
Trials supporting the Safety only				
<b>DIA3010 Older Adults</b>	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects 55 to 80 years of age, inclusive; HbA1c 7 to 10% inclusive	Cana 100 mg: 241 Cana 300 mg: 236 Placebo: 237	104 weeks (26-week placebo-controlled, core double-blind period plus a 78-week placebo-controlled, extension double-blind period)
<b>DIA3014*</b>	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects who are Chinese or other Asian ethnicity on metformin or metformin + SU; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 223 Cana 300 mg: 227 Placebo: 226	18 weeks

<sup>a</sup>Subjects assigned to placebo were switched to sitagliptin during the double-blind extension period  
Abbreviations: Cana=canagliflozin; SU=sulfonylurea; AHA=antihyperglycemic agent; CV=cardiovascular; QD=daily; BID=twice daily

\*Although completed, study 3014 did not contribute efficacy data for this NDA review because it was conducted entirely outside the U.S.

Source: Modified from Table 2, Clinical Review dated November 1, 2013

## 5.2 Review Strategy

### *Efficacy review*

The modeling data (i.e., exposure-response analysis) provided in this resubmission to bridge the efficacy between QD and BID dosing regimen for canagliflozin are being reviewed by the Office of Clinical Pharmacology reviewers. Please see their finalized review for details and conclusion. No new efficacy data from clinical trials in support of FDC was submitted for this NDA.

### *Safety review*

The majority of data contributing to the safety review were reviewed in the original NDA submission. For this resubmission, I reviewed the following completed study reports (CSRs): DIA3009, DIA3014, and DIA3010 (see Table 1), as well as blinded safety data from ongoing trials (i.e., DIA3011, DIA1056, DIA4002) that were submitted as a safety update for this resubmission, with the cut-off date of November 30, 2013. Since safety data of the primary treatment period for DIA3009 and DIA3010 were already reviewed during canagliflozin NDA 204-042, I only reviewed safety data from the extension periods.

### *Data submitted but not relevant to this review*

The applicant submitted blinded safety data from ongoing trials, DIA3011, DIA1056, DIA4002, and DIA3008, with cut-off date of November 30, 2013. However, since the data from these trials remain blinded, it is difficult to evaluate these results, and the results will not be presented in this review.

(b) (4)



In addition, an English translation of text portion of Clinical Study Reports (CSRs) for 5 trials conducted by Mitsubishi Tanabe Pharma Corporation (MTPC) was included in this resubmission. MTPC is developing canagliflozin for Japan, Taiwan, and Indonesia only. These were reviewed, but not presented, as these trials were uncontrolled, and there were no new safety findings of concern.

### *Deleted sections in this review*

The following subsections are deleted in this review since they were not applicable with this resubmission:

- All subsections under Section 6, Review of Efficacy;
- Subsections under 7.2 (7.2.2 through 7.2.6), under 7.4 (7.4.2 through 7.4.6). Since a larger pool of laboratory data related to canagliflozin was previously reviewed, only relevant laboratory findings related to specific adverse events of concern were discussed in relevant safety sections

### **5.3 Discussion of Individual Studies/Clinical Trials**

I will only briefly discuss clinical trials that contributed data to the safety evaluation (see Section 7).

DIA3014 was a Phase 3, double-blind, randomized, placebo-controlled, 3-arm, parallel group, 18-Week multicenter trial conducted at 36 centers in Asia to evaluate the efficacy, safety, and tolerability of canagliflozin (100 mg and 300 mg) compared to placebo in the treatment of subjects with T2DM with inadequate glycemic control on metformin alone or in combination with a sulfonylurea (SU). The primary objectives of this trial were to assess the effect of canagliflozin 100 mg and 300 mg, each dose compared to placebo on the change in HbA1c from baseline to Week 18, and to assess the safety and tolerability of canagliflozin. A total of 678 Chinese and other Asian adult subjects with T2DM who had inadequate glycemic control (HbA1c of 7 to 10.5%, inclusive) on metformin alone (n=331) or metformin plus SU (n=347) were randomized 1:1:1 ratio to either canagliflozin 100 mg QD, canagliflozin 300 mg QD, or placebo for 18 weeks. Subjects were stratified according to whether they were taking metformin alone or in combination with an SU. This trial was completed after the 4MSU.

Safety data from the controlled, non-voluntary extension period from the trials 3009 and 3010 were also reviewed, although it should be noted that DIA3010 provides long-term safety data on canagliflozin alone and not in combination with metformin:

DIA3009 was a Phase 3, double-blind, randomized, active-controlled, 3-arm, parallel-group, multicenter trial with 104-week double-blind treatment period (52-week active-controlled, core double-blind period followed by a 52-week active-controlled, extension double-blind period) to evaluate the efficacy, safety, and tolerability of canagliflozin (100 mg and 300 mg) compared to glimepiride in the treatment of subjects with T2DM with inadequate glycemic control on metformin monotherapy. A total of 1452 subjects were randomized 1:1:1 ratio to either glimepiride, canagliflozin 100 mg, or canagliflozin 300 mg. Although the primary analysis was conducted at Week 52 for efficacy, subjects were to continue until the end of treatment period of Week 104.

DIA3010 was a Phase 3, double-blind, randomized, placebo-controlled, 3-arm, parallel group, multicenter trial with a 104-week double-blind treatment period (26-week

placebo-controlled, core double-blind period followed by a 78-week placebo-controlled, extension double-blind period) to evaluate the efficacy, safety, and tolerability of canagliflozin (100 mg and 300 mg) compared to placebo in the treatment of older subjects with T2DM with inadequate glycemic control on any glucose lowering therapy. A total of 716 subjects were randomized 1:1:1 ratio to either placebo, canagliflozin 100 mg, or canagliflozin 300 mg. Although the primary analysis was conducted at Week 26 for efficacy, subjects were to continue until the end of treatment period of Week 104.

## **6 Review of Efficacy**

### **Efficacy Summary**

No new clinical efficacy data were submitted in support of FDC with resubmission. See Clinical Review dated November 1, 2013 for discussion of efficacy results relevant for this NDA.

## **7 Review of Safety**

### **Safety Summary**

My review of safety data from a newly initiated and completed Phase 3 trial (DIA3014), and safety update with data from the extension periods of DIA3009 and DIA3010 did not show any new safety concern.

### **7.1 Methods**

#### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

I reviewed the safety data from new trial DIA3014, and new safety data from the extension period of DIA3009 and DIA3010. The extension period for DIA3009 and DIA3010 were controlled and nonvoluntary.

#### **7.1.2 Categorization of Adverse Events**

Adverse events were categorized using MedDRA Version 15.1 for DIA3009 and DIA3004, and Version 16.0 for DIA3010.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of clinical trials for safety was not done in this resubmission, as evaluation of pooled safety data to evaluate the safety for the use of canagliflozin with metformin was already done during my review of initial NDA submission where I reviewed the safety of a pooled dataset (DS1-M) of three Phase 3 trials where subjects received canagliflozin with background metformin therapy (DIA3002, DIA3006, and DIA3012). The new additional safety data in this resubmission was relatively small in comparison and did not warrant another pooling.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

DIA3009: The overall subject exposure (regardless of rescue) for subjects in the extension safety analysis set (i.e., during the extension period) was similar across treatment groups: 723 subject-years in glimepiride compared to 760 and 723 subject-years in canagliflozin 100 mg and 300 mg groups, respectively.

DIA3014: The overall subject exposure for subjects was similar across treatment groups: 77 subject-years in placebo compared to 75 subject-years in each canagliflozin treatment groups. The overall exposure of subjects by background therapy was not notably different in the overall study population. The total exposure for those on background metformin alone was 37 subject-years in placebo and each canagliflozin treatment groups. The total exposure for those on background metformin+SU was 40 subject-years in placebo compared to 39 subject-years in canagliflozin 100 mg group and 38 subject-years in canagliflozin 300 mg group.

DIA3010: The overall subject exposure (before rescue) for subjects in the extension safety analysis set (i.e., during the extension period) was slightly higher in the canagliflozin treatment groups: 245 subject-years in placebo compared to 372 and 359 subject-years in canagliflozin 100 mg and 300 mg groups, respectively.

## 7.3 Major Safety Results

### 7.3.1 Deaths

DIA3009: During the extension period, 4 deaths were reported, 3 subjects in the canagliflozin 100 mg group and 1 subject in the canagliflozin 300 mg group. After

reviewing the narratives the events related to deaths in the following 3 subjects did not appear to be related to the study drug: one subject who received canagliflozin 300 mg died due to road traffic accident (subject 902765); one subject who received canagliflozin 100 mg died due to chemical poisoning (subject 901302); and one subject who received canagliflozin 100 mg died due to intracranial hemorrhage after a road traffic accident.

The narrative of one subject who experienced acute renal failure with pulmonary embolism found upon autopsy is provided here:

*Subject 902200 (reported term: pulmonary embolism, acute renal failure):* A 49 year old man with BMI of 42.1 kg/m<sup>2</sup> and history of hypertension experienced a headache and blood pressure of 180/80 mmHg and blood glucose of 5 mmol/L on Day 545. He took an additional dose of indapamide/perindopril erbumine and felt better. About 8 hours later, he had nausea and abdominal pain, and was brought to the emergency room, where he was diagnosed with acute renal failure. On Day 546 (04:00 hr), he was transferred to another hospital and reported to be agitated and disoriented. He died at 8:45 hr on Day 546 during preparation of emergency dialysis. The autopsy showed a massive pulmonary thromboembolism/blood obstruction in the pulmonary arteries, edema of cerebrum and lungs, thickening of left ventricles, generalized atherosclerosis in the stage of complicated plaques, acute congestion of internal organs, and no traumatic injuries and no alcohol was noted in the blood. The cause of death was determined to be massive pulmonary embolism.

DIA3014: No deaths occurred during the 18-week double-blind treatment phase.

DIA3009: Six deaths were reported during the extension period, 4 subjects in the canagliflozin 100 mg group and 2 subjects in the placebo group. Of 4 deaths in the canagliflozin group, three died due to stroke and myocardial infarction, and one (subject 101787) died due to pulmonary embolism on Day 498. Subject 101787 had history of hypertension and was a 62 year old postmenopausal woman.

**Reviewer's comment: Overall, there are two deaths related to pulmonary embolism (PE), one each from DIA3010 and DIA3009 during the extension period, but both subjects had risk factors (i.e., hypertension, obesity). Venous thromboembolic events (VTE) were adverse events of concern that were independently adjudicated in the canagliflozin program, and were not shown to be of concern based on our review of large safety data pool. These two additional cases of PE with risk factors do not appear to pose new concern at this time.**

### 7.3.2 Nonfatal Serious Adverse Events

DIA3009: During the extension period, the overall incidence of nonfatal serious adverse events (SAEs) was higher in the glimepiride group (8.1% [31/381]) compared to the

canagliflozin groups (6.1% [24/393] and 5.8% [22/377] in the canagliflozin 100 mg and 300 mg groups, respectively). The only SAEs occurring in more than 2 subjects in the canagliflozin 100 mg group was chronic cholecystitis in 2 subjects. No SAEs occurred in more than 2 subjects in the canagliflozin 300 mg group.

**Reviewer's comment: Review of reported SAE table during the extension period of DIA3009 (Table 55 of CSR DIA3009) did not indicate any new safety concern with canagliflozin at this time, and thus narratives are not presented in this review.**

DIA3004: The overall incidence of SAEs was low in this study and similar in the canagliflozin groups (2.2% [5/223] and 1.8% [4/227] in 100 mg and 300 mg groups, respectively) compared to the placebo group (1.8% [4/226]). No specific SAE term was reported in more than one subject.

**Reviewer's comment: Narratives for SAEs from DIA3004 are not presented here because except for one event of hypoglycemia with canagliflozin 300 mg, other events do not pose safety concern at this time. Hypoglycemia, although at a lower rate compared to some other anti-diabetic agent (e.g., sulfonylurea), is an expected event with canagliflozin.**

DIA3010: During the extension period, the overall incidence of serious adverse events (SAEs) was 15.5% (30/193) with placebo compared to 13.8% (31/224) and 17.4% (36/207) with canagliflozin 100 mg and 300 mg, respectively. There were no discernable pattern of SAEs in canagliflozin groups, and except for some terms in the Cardiac Disorders System Organ Class and nephrolithiasis, the majority of SAEs occurred in no more than one subject in any single treatment group.

Nephrolithiasis occurred in 3 subjects and 1 subject from canagliflozin 100 mg and 300 mg groups, respectively, and none in the placebo group; none of these led to study discontinuation. Four subjects who experienced serious nephrolithiasis are described:

- Subject 100832 (canagliflozin 100 mg): A 62-year-old man with active history of back pain was hospitalized for back pain on Day 297. No abnormalities were found on chest, abdominal, hip X-ray, or CT scan of kidneys, ureters, and bladder. He was diagnosed with nephrolithiasis. Treatment was temporarily discontinued and he was treated with pain medication; he underwent lithotripsy on Day 307 and event resolved. Treatment with study drug was restarted on Day 326, and he completed the study on Day 732.
- Subject 101717 (canagliflozin 100 mg): A 65-year-old man experienced lower abdominal pain on an unspecified day before the onset of nephrolithiasis. On Day 325, he was admitted to the hospital and left flank tenderness was noted on exam, and he was diagnosed with nephrolithiasis. He underwent extra corporeal

shockwave lithotripsy and insertion of JJ stent, and received medical treatment. Nephrolithiasis was resolved on Day 326, he continued the study drug, and completed the study on study drug on Day 729.

- Subject 101230 (canagliflozin 100 mg): A 59-year-old man experienced kidney infection and nephrolithiasis on Day 468; kidney infection resolved on Day 472. On Day 481, he presented to emergency room with complaints of moderate left abdominal/flank pain with loss of appetite, costovertebral angle tenderness, and presence of leukocytes in urine. He was again diagnosed with nephrolithiasis and UTI on the same day. He underwent stone removal, a stent was placed in the kidney, and he received medical treatment. Study drug was interrupted on Day 481 and restarted the following day. Nephrolithiasis resolved on Day 482, and a new event of nephrolithiasis recurred. He was treated with Percocet and lidocaine. On Day 495, he was diagnosed with renal colic, and he underwent extracorporeal shock-wave lithotripsy with showed left renal stone with indwelling double J stent. On Day 501, he was diagnosed with staphylococcal UTI with positive urine culture. On Day 510, cystoscopy and removal of stone was done with removal of unilateral JJ stent via cystoscopy. The staphylococcal UTI resolved on Day 510, and the event of renal colic and urethral discharge resolve don Day 532. On Day 544, he underwent KUB which showed persistent left distal urethral stones. Nephrolithiasis resolved on Day 585. He completed the study drug treatment on Day 727.
- Subject 101857 (canagliflozin 300 mg): A 66-year-old woman with history of renal calculus and urinary tract infection (UTI) experienced 2 episodes of UTI on Days 236 and 273 (with resolution 3-7 days). On Day 316, she was hospitalized with complaints of recurrent UTI and backache, and she was diagnosed with SAE of nephrolithiasis. The ultrasound confirmed renal calculus in the right kidney, treatment with the study drug was discontinued, and she had a cystoscopy and pyelogram with insertion of a stent. She received treatment, and nephrolithiasis resolved on Day 321. Study drug was restarted on Day 323, and she completed the study on study drug on Day 729.

**Reviewer's comment: Frequent urinary tract infections are one of less common causes of nephrolithiasis, and both subjects 101230 and 101857 had recurrent UTI concurrent with nephrolithiasis. Subject 101857 also had history of renal calculus. None of these subjects discontinued the study, and completed the study on study drug without recurrence of nephrolithiasis.**

Nephrolithiasis is a concerning adverse event that may result from decreases in serum urate. In DIA3010, decreases in the mean percent change from baseline in serum urate was seen at Week 104 in the canagliflozin 100 mg and 300 mg groups (-7.1% and -8.9%, respectively) compared to the placebo group (-0.5%). Similarly, the incidence of subjects meeting outside pre-defined limit criteria (PDL) for serum urate (i.e., <lower

limit of normal and decreased >25% from baseline) was higher in canagliflozin groups (1.7% [4/236] and 3.1% [7/226] in 100 mg and 300 mg group, respectively) compared to the placebo group (0.9% [2/228]). This finding is similar to what was noted during the canagliflozin NDA 204-042 review, where decreases in the mean percent change from baseline in serum urate was observed with canagliflozin compared to placebo in a pooled safety dataset DS1 (-10.1% with 100 mg and -10.6% with 300 mg compared to 1.9% with placebo), and the incidence of subjects meeting the PDLC was 1.9% in each canagliflozin group compared to 0.2% in the placebo group. The decreases in serum urate with canagliflozin was noted to be maximal or near maximal at the first ascertained timepoint, Week 6, and remained stable through Week 26 in DS1 (a pooled dataset of all placebo-controlled Phase 3 trials in canagliflozin NDA 204-042). This was similarly observed in DIA3010, where the maximal decrease in serum urate occurred at Week 6 and remained stable through Week 104.

**Reviewer's comment: The maximal decrease in serum urate occurred by Week 6 and remained stable, whereas the imbalance in nephrolithiasis was not observed during the core treatment period of DIA3010 (i.e., during the first 26 weeks), and only during the extension period (i.e., 26 to 104 weeks) on Days 297-468 (approximate Weeks 42-66).**

Table 2 summarizes the overall incidence of nephrolithiasis (with the Preferred Term 'Nephrolithiasis') from DIA3010 (core, extension, and the entire period) and from 4 large pooled safety datasets from canagliflozin NDA 204-042. Although a slightly imbalance in the incidence of nephrolithiasis not favoring canagliflozin 100 mg compared to placebo was seen in DIA3010 (mainly during the extension period), this was due to a small difference in the number of events and the incidence was not higher with canagliflozin 300 mg. Similar trend in the incidence of nephrolithiasis was seen in DS3 and DS4, but the imbalance was even smaller (see section 7.1.3 of Clinical Review of NDA 204-042 for details of pooled dataset).

**Table 2: Incidence (% [n/N]) of Nephrolithiasis in DIA3010 Compared to DIA3008 and Other Pooled Safety Datasets**

	Placebo*	Cana 100 mg	Cana 300 mg	Cana Total
<b>DIA3010 core period</b> (Day 1 to Week 26)	0.4% (1/237)	0.4% (1/241)	0 (0/236)	0.2% (1/477)
<b>DIA3010 extension period</b> (Weeks 26 to 104)	1.6% (3/193)	2.2% (5/224)	0.5% (1/207)	1.4% (6/431)
<b>DIA3010 entire period</b> (Day 1 to Week104)	1.7% (4/237)	2.5% (6/241)	0.4% (1/236)	1.5% (7/477)
<b>DS1</b> (All Placebo-controlled trials)	0.2% (1/646)	0 (0/883)	0 (0/834)	0 (0/1667)
<b>DS2</b> (All subjects with moderate renal function)	0.8% (3/382)	0.3% (1/338)	0.3% (1/365)	0.3% (2/703)
<b>DS3*</b> (All Active- and Placebo-controlled trials)	0.3% (11/3262)*	0.5% (15/3092)	0.2% (5/3085)	0.3% (20/6177)
<b>DS4*</b> (All Active- and Placebo-controlled trials through January 31, 2012)	0.6% (18/3262)*	0.7% (21/3092)	0.2% (6/3085)	0.4% (27/6177)

\*Non-Canagliflozin group (both placebo and active-control group was combined for DS3 and DS4 as non-canagliflozin group)

Sources: CSR DIA3010 Week 104, Output DAE01R\_EXT; CSR DIA3010 Week 26, Output DAE01RM\_Core; CSR DIA3008-INT, Output DAE01E; ISS Output DAE01R\_01, DAE01R\_02, DAE01R\_03, DAE01R\_04

**Reviewer’s comment: A higher incidence of SAEs related to nephrolithiasis was observed with canagliflozin compared to placebo in DIA3010, mainly during the extension period (i.e., Weeks 26-104) and mainly in the canagliflozin 100 mg group. Although the overall incidence of nephrolithiasis was slightly higher with canagliflozin 100 mg compared to placebo in DIA3010 during extension period as shown in Table 2, the imbalance is due to small number of events and was not seen with the higher dose of canagliflozin. In addition, the largest safety pooled dataset of Phase 3 canagliflozin trials (DS4) did not show concerning increase in the incidence of nephrolithiasis with canagliflozin.**

### 7.3.3 Dropouts and/or Discontinuations

DIA3009: During the extension period, the incidence of AEs leading to discontinuation was most frequent with canagliflozin 300 mg: 2.1% (8/381) in the glimepiride group, 1.3% (5/393) and 3.7% (14/377) in the canagliflozin 100 mg and 300 mg group, respectively. The only AEs leading to discontinuation occurring in more than 2 subjects was in the canagliflozin 300 mg group, where 4 subjects experienced decreased glomerular filtration rate (GFR) and 3 subjects experienced renal failure.

**Reviewer’s comment: Although there are more renal-related AEs leading to discontinuation with the canagliflozin 300 mg group during the extension period, the overall renal-related adverse events occurred slightly more in the glimepiride group (3.1% [12/381]) compared to the canagliflozin group (2.3% [9/393] and 2.4%**

**[9/377] in the 100 and 300 mg groups, respectively). See section 6.1.6.6 of CSR for DIA3009 for details. Decline in GFR with the higher dose of canagliflozin, and an increased incidence of renal-related adverse reactions including renal failure are labeled for canagliflozin. Narratives for AEs leading to discontinuations are not presented in this review because there are no concerning events needing further exploration.**

DIA3004: The overall incidence of AEs leading to discontinuation was low and slightly higher in the canagliflozin groups (2.7% [6/223] and 3.1% [7/227] in 100 mg and 300 mg groups, respectively) compared to the placebo group (1.3% [3/226]). No specific AE term leading to discontinuation was reported in more than one subject, except for decreased GFR and blood creatinine increased (each reported in 2 subjects in the canagliflozin 100 mg group), rash (2 subjects in the canagliflozin 300 mg group), and hypoglycemia (2 subjects in the canagliflozin 300 mg group).

**Reviewer's comment: Decreased renal function (i.e., decreased GFR and increase in creatinine), rash due to hypersensitivity, and hypoglycemia are all labeled events with canagliflozin. As a result, narratives are not presented here since there are no new safety concerns.**

DIA3010: During the extension period, the incidence of AEs leading to discontinuation was 3.6% (7/193) in the placebo group, 2.2% (5/224) in the canagliflozin 100 mg group, and 3.9% (8/207) in the canagliflozin 300 mg group. The only AE leading to discontinuation occurring in more than 1 subject was back pain in the canagliflozin 300 mg group (2 subjects) compared to none in either placebo or canagliflozin 100 mg groups.

One subject (100299) with back pain on Day 319 had a history of cervical discectomy. The other subject (101775) was a 64-year old postmenopausal woman with a complicated medical history including diabetic neuropathy, breast cancer requiring lumpectomy, and irritable bowel syndrome who experienced low back pain on Day 222 and discontinued the study drug.

#### 7.3.4 Significant Adverse Events

No new significant adverse events were noted.

#### 7.3.5 Submission Specific Primary Safety Concerns

On January 30, 2014, we requested the applicant to explore the potential differences in the night-time occurrence of polyuria/nocturia, hypovolemia/hypotension and fall related adverse reactions depending on timing of administration in the overall canagliflozin program, given that the FDC product will be recommended for twice daily use.

The applicant provided a response in this resubmission that the specific analysis to assess nighttime occurrence of these adverse events between QD and BID was not possible because the time at which an AE related to osmotic diuresis, volume depletion, or falling was not collected in the canagliflozin program.

There was no incidence of nocturia, which is an adverse event with a nighttime occurrence, in DIA2003 or DIA2001, which contained BID dosing arms of canagliflozin (see Table 1). The incidence of nocturia in large pooled safety datasets (i.e., DS1, DS3) with canagliflozin was also very low, as shown in Table 3, with only slight imbalance across treatment arms.

**Table 3: Incidence (% [n/N]) of Nocturia in Pooled Safety Datasets**

	Placebo*	Cana 100 mg	Cana 300 mg	Cana Total
<b>DS1</b> (All Placebo-controlled trials)	0.2% (1/646)	0.4% (3/883)	0.1% (1/834)	0.2% (4/1667)
<b>DS3*</b> (All Active- and Placebo-controlled trials)	0.3% (10/3262)*	0.5% (14/3092)	0.4% (13/3085)	0.4% (27/6177)

\*Non-Canagliflozin group (both placebo and active-control group was combined for DS3 as non-canagliflozin group)  
Sources: ISS Output DAE01R\_01, DAE01R\_03, DAE01R\_04

In DIA2003, osmotic diuresis-related adverse events were reported in 7 (7.5%) subjects in the canagliflozin 150 mg BID group compared to none in either canagliflozin 50 mg BID or placebo group. The adverse events in these subjects included pollakiuria (n=4), micturition urgency (n=1), dry mouth (n=1), and thirst (n=1). None of these were serious or led to study discontinuation. No volume depletion-related adverse events, fracture, or fall were reported in DIA2003.

In DIA2001, osmotic diuresis-related adverse events occurred in 3 (5%) subjects in the canagliflozin 300 mg BID group, 1 to 7 (2 to 11%) subjects in the canagliflozin QD groups, and 2 (3%) subjects in the placebo group. None of these were serious or led to study discontinuation. Volume depletion-related events were reported only in the QD groups (one subject), and none in the canagliflozin 300 mg BID groups or placebo group. One adverse event of fracture was reported in canagliflozin 300 mg BID group and one adverse event of fall was reported in the placebo group.

**Reviewer's comment: Increased urination (which also included the preferred term "nocturia") with canagliflozin is a labeled adverse reaction. Since canagliflozin was given once daily in clinical trials and this FDC is proposed to be given twice daily, there were some concerns that administration of canagliflozin in the evening may lead to increased incidence of nocturia, volume-depletion events, or fall. Only 2 small Phase 2 trials administered canagliflozin BID, and safety data from these trials do not appear to present safety concern at this time, although it should be noted that the sample size for these Phase 2 trials are relatively small to thoroughly evaluate these safety issues. However, given that**

**the BID dosing will administer 50% of normal total canagliflozin dosing, and based on these overall safety data, I do not believe that this theoretical risk should affect the approvability of this FDC.**

## **7.4 Supportive Safety Results**

### 7.4.1 Common Adverse Events

DIA3009: Upon review of AEs during the extension period, the only AE with a higher incidence in the combined canagliflozin group compared to the glimepiride group was influenza (2.7% versus 1.3%), urinary tract infection (5.2% versus 4.7%), and back pain (2.3% versus 2.1%). The incidence of urinary tract infection (UTI) was reported higher in the canagliflozin 100 mg group (6.4% [25/393]) compared to the 300 mg group (4.0% [15/377]) and glimepiride group (4.7% [18/381]). Higher incidence of influenza was seen in both canagliflozin groups (2.8% [11/393] and 2.7% [10/377] in 100 mg and 300 mg groups, respectively) compared to the glimepiride group (1.3% [5/381]).

**Reviewer's comment: UTI is already in the canagliflozin labeling. The imbalance in the incidences of influenza and back pain between treatment groups was small and does not appear to be of concern at this time.**

DIA3004: The overall incidence of AEs was similar across treatment groups, 42% [95/226] in placebo, and 39% [86/223] and 43% [98/227] in the canagliflozin 100 mg and 300 mg groups, respectively. As expected, the incidence of hypoglycemia was higher in the canagliflozin groups (9.0% [20/223] and 7.5% [17/227] in 100 mg and 300 mg groups, respectively) compared to the placebo group (4.0% [9/226]).

Review of incidences of adverse events by Preferred Term did not show any new safety concern, except an increased incidence of thrombocytopenia. Seven (1.6%) subjects in the canagliflozin groups (5 and 2 subjects in the 100 mg and 300 mg groups, respectively) and two (0.9%) subjects in the placebo group reported 'thrombocytopenia' or 'platelet count decreased'.

**Reviewer's comment: The imbalance in the incidence of thrombocytopenia or decreased platelet count between treatment groups was small, and none of these events were serious or led to study discontinuation. My review of laboratory results from DIA3004 showed no difference in the mean change from baseline in platelet count or in the incidence of outliers between treatment groups (see section 6.2 of CSR DIA3014). Thus this did not appear to be of safety concern at this time.**

DIA3010: Upon review of AEs during the extension period, the only adverse event with a higher incidence in the combined canagliflozin group compared to the placebo group

was bronchitis (3.7% versus 1.6%), nasopharyngitis (15.1% versus 11.4%), urinary tract infection (11.6% versus 8.8%), back pain (8.4% versus 5.7%), and balanoposthitis (2.1% versus 0). These are all labeled events for canagliflozin.

## 7.7 Additional Submissions / Safety Issues

None.

## 8 Postmarket Experience

On February 13, 2014, the applicant submitted a summary of cumulative postmarketing data for canagliflozin with a cutoff date of November 30, 2013 that was inadvertently omitted in the February 10, 2014 NDA resubmission. Since canagliflozin/metformin IR FDC has not yet been marketed in any country, the postmarketing exposure and safety data pertains to canagliflozin as a single agent. As of November 30, 2013, canagliflozin was approved for marketing and launched in US (April 2, 2013) and Australia (November 19, 2013).

From their distribution data, the applicant estimated the following world-wide patient exposure (from April 1, 2013 to November 30, 2013):

Person Days (100 mg tablets)	Person Days (300 mg Tablets)	Total Person-Days	Total Person-Years
(b) (4)	(b) (4)	(b) (4)	66,865

From March 29, 2013 through November 30, 2013, 1178 spontaneous cases reported 2033 adverse events. Of these, 387 were serious adverse events. Review of reported serious adverse events did not identify any new safety concerns (see Attachment 1 of the Safety Update Addendum 1). SAEs reported 10 or more times included dehydration (n=31), urinary tract infection (n=17), blood creatinine increased (n=13), renal failure acute (n=13), hypotension (n=11), renal failure (n=11), and glomerular filtration rate increased (n=10). All of these are labeled events for canagliflozin.

Five were fatal events, which included 2 cases of myocardial infarction, 2 cases of deaths (unspecified), and one case of adverse event (unspecified). Myocardial infarction (MI) occurred in two subjects with significant risk factors (i.e., hyperlipidemia and family history of coronary artery disease in one; hypertension, hyperlipidemia and obesity in the other), which makes it difficult to attribute the MI to canagliflozin. Three other events were unspecified events and not evaluable.

In addition to spontaneous reports, 307 cases were solicited, reporting 742 adverse events of which 53 were serious. No death was reported. SAEs reported more than twice included dehydration (n=5) and blood glucose increased (n=3), which are expected events with canagliflozin.

## **9 Appendices**

### **9.1 Literature Review/References**

None.

### **9.2 Labeling Recommendations**

Comments regarding labeling are presented throughout the review, and a line-by-line labeling review will be conducted separately.

### **9.3 Advisory Committee Meeting**

Not conducted.

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/s/  
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HYON J KWON  
07/23/2014

LISA B YANOFF  
07/23/2014

MEMO TO FILE

NDA 204353, SD #17 (eCTD sequence #0016)

Product: Canagliflozin/metformin immediate-release fixed dose combination

Applicant: Janssen Research and Development, LLC

Submitted: January 3, 2013

RE: Safety Update Proposal for NDA Resubmission

**Background:**

The applicant received a Complete Response Letter (CRL) for the canagliflozin/metformin immediate-release fixed dose combination NDA (204353) for the treatment of type 2 diabetes mellitus (T2DM) on December 21, 2013. In the CRL, we requested a safety update to “include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level”.

The latest integrated safety data for this NDA was the 4-month safety update (4MSU) on April 5, 2013, which had data cut-off date of December 2012. The following 4 studies were ongoing at the time of this 4MSU:

- DIA3008 (CANVAS, or cardiovascular study): This study is still ongoing and blinded data is being monitored. In 4MSU, all unblinded, on-treatment subject data were included;
- DIA3009 (add-on to metformin study): The database lock for this study was February 13, 2013, which was 6 weeks after the 4MSU data cut-off date. All unblinded, on-treatment subject data were included in the integrated 4MSU, but data from subjects completing their 30-day off study drug follow-up visit was not included. The CSR for DIA3009 was submitted to IND 76,479 (SN0519) on August 30, 2013 with cross-reference to IR FDC IND 110,545 (SN0264).
- DIA3010 (study in older adults): The database lock for this study was June 28, 2013, 6 months after the 4MSU data cut-off date. The applicant indicated that the 4MSU included 94.1% of all on-treatment subject data, and the remaining 5.9% were included in the CSR for DIA3010 which was submitted to IND 76,479 on November 20, 2013 (SN0539) with cross-reference to IR FDC IND 110,545 (SN0274).
- DIA3014 (study in T2DM subjects living in Asia): This 18-week study was conducted in Asian subjects on a background of metformin or metformin plus sulfonyleurea, (b) (4) was not conducted under the US IND. This study was completed after 4MSU.

Since the submission of 4MSU, the following two studies were initiated and are currently ongoing (subjects remain blinded):

- DIA3011 is investigating canagliflozin and metformin used as monotherapy or in combination in subjects with T2DM not currently receiving antihyperglycemic agent.
- DIA1056 is a study in normal healthy subjects to assess urinary glucose excretion and post-prandial glucose excursion in response to canagliflozin after multiple doses of canagliflozin and dapagliflozin.
- DIA4002 is a Phase 4 study evaluating the change in blood pressure in subjects with hypertension and T2DM. This study is not being conducted under the US IND because it is exempt per 21 CFR 312.2(b). The study was initiated in Q4 2013 and 10 subjects were randomized through the end of 2013.

Also, since 4MSU submission, the final report for [REDACTED] (b) (4)

[REDACTED] In addition, final reports for 5 Mitsubishi Tanabe Pharmaceutical Corporation (MTPC) studies have become available since 4MSU (TA-7284-05, -06, -07, -08, -10). MTPC is developing canagliflozin in Japan, Taiwan, and Indonesia, and the applicant do not have access to full dataset to MTPC studies and have not pooled the MTPC safety data with their data throughout their submissions.

**Safety Update Proposal:**

The applicant proposes to provide A-E below to satisfy items 1-6 under Safety Update section from the CRL letter:

- A. For ongoing studies DIA3008, DIA3011, DIA4002, and DIA1056, the applicant proposes to not unblind subject-level data for inclusion in the integrated safety summary:
  - For DIA3008 and DIA3011, IDMC monitors subject safety and the applicant proposes to include correspondence from the IDMC since 4MSU data cut-off date;
  - For DIA3011 and DIA1056, the applicant will provide a brief description of study, and include proportion of all subjects with adverse events, deaths, serious adverse events (SAEs), and adverse dropouts, along with listings of deaths, SAEs, and adverse dropouts. The data will be blinded, however.
  - For DIA3008, an updated incremental blinded output since 4MSU through a cutoff date of November 30, 2013 will be provided which will include proportion of subjects with deaths, SAEs, adverse dropouts along with listing of these subjects.
  - No data will be provided for DIA4002 since only 2 subjects have been randomized as of November 30, 2013.
- B. For completed studies since 4MSU, DIA3009 and DIA3010, the applicant proposes to not update the integrated safety analysis with data from these studies since additional safety data after

4MSU is small and no new safety issues have been identified from these studies. The CSRs from these studies have been submitted to canagliflozin IND and the applicant proposes to include these CSRs with the NDA resubmission.

- C. The applicant stated that no new safety issues were identified in DIA3014. DIA3014 had 678 subjects randomized to the study drug with 150 subject-years of exposure to canagliflozin, compared to the pooled dataset of 3 placebo-controlled 26-week studies in subjects on canagliflozin with metformin (DS1-M) which included 1731 subject with 590 subject-years of exposure to canagliflozin. The applicant proposes to include DIA3014 CSR in the NDA resubmission and not provide an updated integrated analysis with DIA3014 data.
- D. The applicant proposes to submit the CSRs for (b) (4) and 5 MTPC studies that have become available since 4MSU.
- E. The applicant proposes to submit study reports for 3 new nonclinical studies since 4MSU (FK10426, FK10427, and TOX10433) and 3 amended nonclinical studies (FK5352, FK7341, and FK7434). The applicant stated that no significant safety issues were seen in these studies.

***Internal comment: I defer to PharmTox Reviewer regarding submission of these nonclinical studies.***

For item 7, the applicant will provide a postmarketing data section with an estimate of the worldwide exposure and a summary of all adverse events from spontaneous reporting and from ongoing post-marketing studies, with a cutoff date of November 30, 2013. Data from interventional clinical studies will not be included.

For item 8, the applicant will include an English translation of the Mexican label (the only non-English label) as well as a copy of the Australian and EU labels in its complete response, as canagliflozin is currently approved in the US, Australia, Mexico, and the EU.

**Reviewer's comment: The applicant's proposal for submission of clinical safety update is reasonable, given that there were no new safety issues found during the review of NDA 204535 (canagliflozin and metformin combination) compared to NDA 204042 (canagliflozin monotherapy), and the 4MSU for this NDA submission included updated integrated summary of safety without any notable new safety findings. I would like to request narratives for subjects who died or had adverse events of interest, as stated below.**

**Action Item:** I recommend communicating the following to the applicant:

- Your overall proposal for updating clinical safety data is reasonable. In addition, we request that you submit narratives for subjects who died, had malignancy of interest (i.e., pheochromocytomas, Leydig cell tumors, renal cell carcinoma), fatal or hemorrhagic/necrotizing pancreatitis, or severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome) since the 4-Month

Safety Update submitted on April 5, 2013. Also, if new or unexpected safety concerns arise from the NDA resubmission, we may request more summaries, narratives, or unblinded data.

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/s/  
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HYON J KWON  
01/10/2014

ALI MOHAMADI  
01/10/2014

## Cross-Discipline Team Leader Review

<b>Date</b>	November 21, 2013
<b>From</b>	Ali Mohamadi, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	204353
<b>Supplement#</b>	
<b>Applicant</b>	Janssen Research and Development, LLC
<b>Date of Submission</b>	December 12, 2012
<b>PDUFA Goal Date</b>	December 12, 2013
<b>Proprietary Name / Established (USAN) names</b>	(b) (4) (canagliflozin/metformin HCl)
<b>Dosage forms / Strength</b>	Oral tablets with the following dosage strengths: Canagliflozin 50 mg/metformin 500 mg release film Canagliflozin 50 mg/ metformin 1000 mg Canagliflozin 150 mg/metformin 500 mg Canagliflozin 150 mg/metformin 1000 mg
<b>Proposed Indication(s)</b>	As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets
<b>Recommended:</b>	Complete response

## • Introduction

(b) (4) is a fixed-dose combination (FDC) tablet that contains two anti-diabetic medications: canagliflozin and metformin (immediate release formulation). This is a 505(b)(2) application for approval of the FDC as 1) an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin; or 2) in patients who are already treated with both individual products dosed as separate tablets. The drug product is dosed twice daily with the following proposed dosage strengths (shown as canagliflozin/metformin): 50 mg/500 mg, 50 mg/1000 mg, 150 mg/500 mg, and 150 mg/1000 mg.

## • Background

Canagliflozin is an orally active, competitive, reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2). Inhibition of SGLT2 reduces renal reabsorption of filtered glucose and increases urinary glucose excretion, thereby lowering plasma glucose levels in patients with T2DM. It was approved for the treatment of T2DM in the US on March 29, 2013 (NDA 204402).

Metformin is an oral biguanide, which decreases production of hepatic glucose, intestinal glucose absorption and improves insulin sensitivity. It was approved for the treatment of T2DM in US as Glucophage (NDA 20357) on March 3, 1995.

The safety and efficacy of the FDC product is supported in this application by Phase 3 trials that were submitted under the original canagliflozin NDA. In the canagliflozin program, six Phase 3 studies evaluated once-daily administration of canagliflozin 100 mg or 300 mg given once daily (QD) in subjects with T2DM on background metformin therapy (alone or in combination with other antidiabetic agents). Because metformin is typically given twice a day for patients with T2DM, the FDC is also proposed to be dosed twice daily (BID), with the canagliflozin component divided to provide the same total daily dose (i.e., 100 mg and 150 mg BID) as currently approved. To support a BID dosing regimen of the FDC product, the sponsor has sought to bridge QD and BID dosing of canagliflozin with an approach that includes a pharmacokinetic/pharmacodynamic (PK/PD) modeling analysis as well as a cross-study comparison of change in hemoglobin A1c (HbA1c) between the original canagliflozin Phase 3 trials, in which the drug product was dosed QD, and a new Phase 2 trial that evaluates BID dosing.

The sponsor's proposed plan to bridge the QD canagliflozin dosing regimen to the proposed BID regimen is a major focus of this review. Whether this plan appropriately bridges the two doses and demonstrates an exposure-response relationship for canagliflozin and HbA1c is pivotal to my assessment of the approvability of this NDA.

- **CMC/Device**

Chemistry, manufacturing and controls data related to the drug substance manufacturing process were found to be acceptable and are detailed in Dr. Sheldon Markofsky's review. The biopharmaceutics reviewer, Dr. Okponanabofa Eradiri, reviewed the dissolution method and dissolution specifications to be used for registration, batch release and stability testing and found them to be acceptable for approval.

- **Nonclinical Pharmacology/Toxicology**

Nonclinical pharmacology and toxicology data were found to support approval of NDA 204353 and are detailed in Dr. Alavi's review.

In brief, the safety of the FDC was supported by a 3-month toxicology (canagliflozin/metformin doses of 4/300, 20/300 and 100/300 mg/kg/day) and an embryofetal development (EFD) study in rats (canagliflozin/metformin doses of 10/300, 30/300, 60/300, 60/0 and 0/300 mg/kg/day). As previously observed with canagliflozin alone, canagliflozin administered as a combination product resulted in a dose-dependent increase in urinary glucose excretion and urine volume and calcium and trabecular bone hyperostosis (at all doses) in Sprague Dawley rats. Furthermore, canagliflozin increased renal tubule and pelvic dilatation as a likely consequence of adaptation to polyuria. The addition of 300 mg/kg metformin had no impact on the toxicity profile of canagliflozin in rats. Furthermore, metformin had no impact on canagliflozin exposure; however, canagliflozin increased metformin AUC exposure by as much as 1.8 fold. Since metformin is primarily excreted by renal filtration, the increase in metformin AUC is likely due to canagliflozin's effect on renal hemodynamics in rats. Based on renal tubule dilatation, a dose of 4 mg/kg constituted the no adverse effect level (NOAEL). There was no safety margin for canagliflozin's effect on renal tubule dilatation, with an exposure multiple of less than unity relative the the clinical dose of 300 mg on an AUC basis. At a NOAEL greater than 300mg/kg, the safety margin for metformin was approximately 9x the maximum clinical dose of 2000mg/kg/day.

In the EFD study, similar to canagliflozin alone, co-administration of canagliflozin with metformin decreased maternal body weight (all doses), and increased the incidence of skeletal variations. The skeletal variations (incomplete, reduced or extra ossification) were likely due to maternal weight loss, and likely represent delayed development. The maternal NOAEL based on weight loss was 10/300 mg/kg while NOAEL for fetal skeletal variation was 60/300 mg/kg. As noted in the 3-month combination study, metformin had no effect on canagliflozin AUC exposure; however, canagliflozin increased metformin exposure by 1.5 fold.

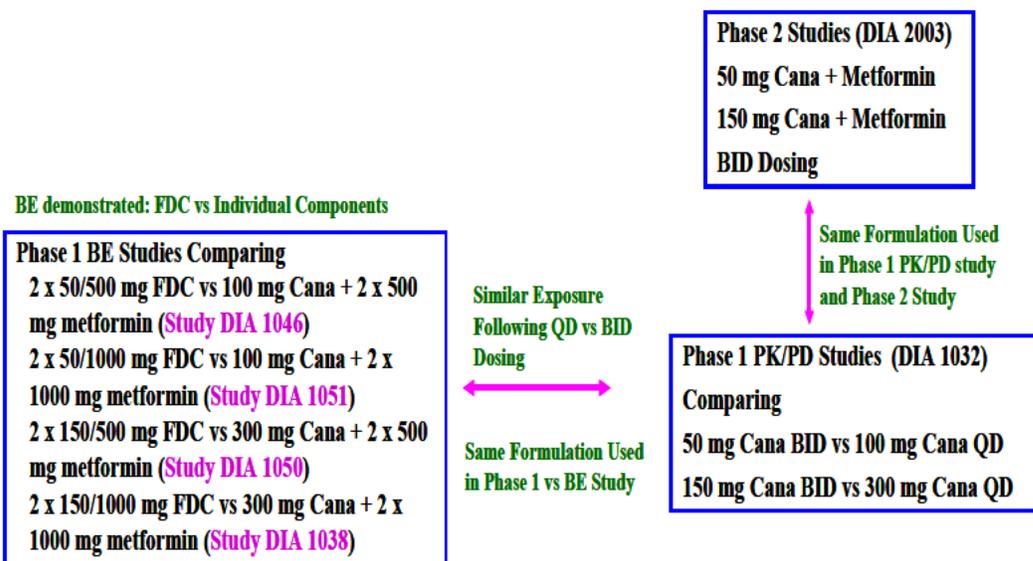
## • Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team recommends a Complete Response to the NDA. For complete details, please refer to the review authored by Dr. Ritesh Jain; a summary of follows.

The sponsor's plan to bridge once daily canagliflozin to twice-daily administration has evolved over time based on the Agency's recommendations. Its initial proposal, as communicated to the Agency at the End of Phase 2 meeting, included:

- Study DIA 2003, a Phase 2, 3-arm, 18-week study to evaluate the safety and efficacy of the twice-daily dosing of 50 mg and 150 mg canagliflozin, relative to placebo, in 273 subjects on a background of metformin.
- Four Phase 1 studies that sought to demonstrate the bioequivalence of the to-be-marketed canagliflozin/metformin tablet to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively]).
- A food effect study (DIA1037) evaluating the effect of food on the to-be-marketed canagliflozin/metformin FDC immediate release tablet (not mentioned further in this review).
- A Phase 1 PK/PD study (DIA1032), to demonstrate that canagliflozin plasma pharmacokinetic and pharmacodynamic responses were similar at the same total daily dose (100 mg or 300 mg) regardless of once- or twice-daily administration.

**Figure 1: Sponsor's initial bridging plan**



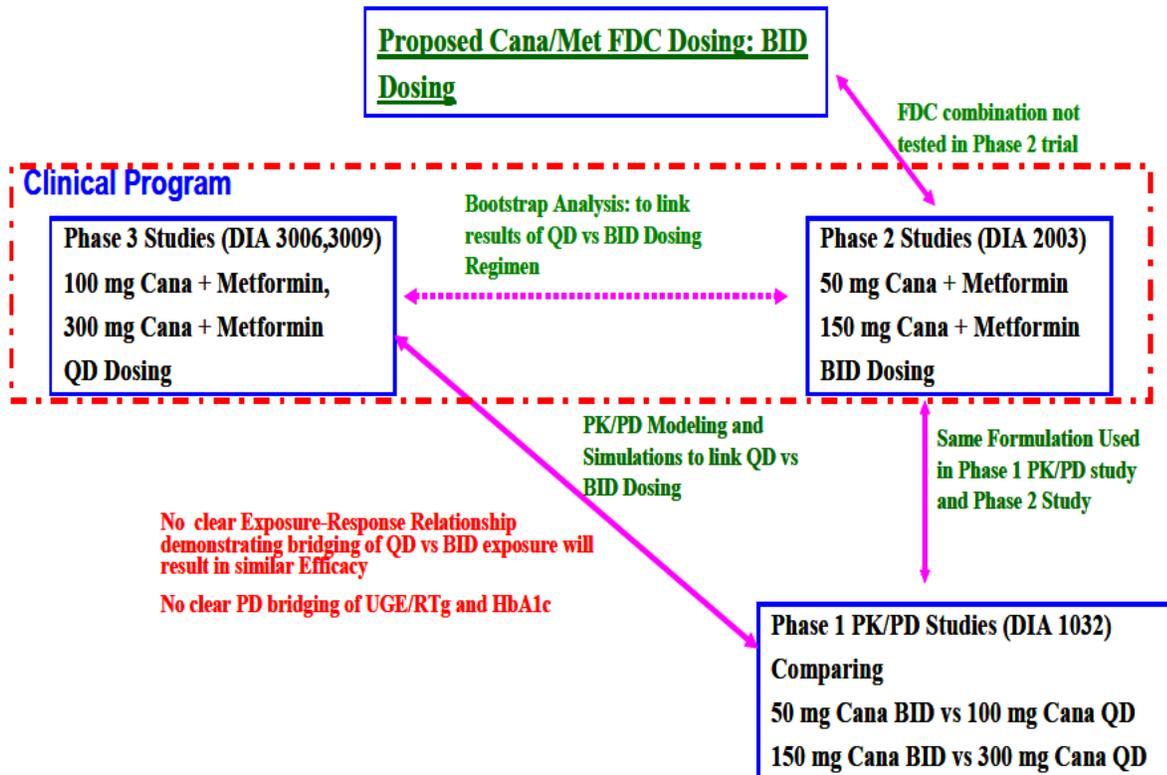
Source: Dr. Ritesh Jain's Clinical Pharmacology Review

Figure 1 above represents the sponsor's initial canagliflozin bridging plan. In its Phase 2 study DIA2003, individual tablets of canagliflozin and metformin were used (one 50 mg canagliflozin tablet for the 50 mg dose and one 100 mg tablet plus one 50 mg tablet over-encapsulated for administration of a single capsule for the 150 mg dose). To link the individual tablets used in Study DIA2003 to the proposed FDC formulation, the sponsor conducted four bioequivalence studies (DIA1046, DIA1051, DIA1050, and DIA1038). To bridge the already-marketed canagliflozin 100 mg and 300 mg once daily tablets to the 50 mg and 150 mg twice daily tablets used in Study DIA2003, the sponsor conducted a Phase 1 PK/PD study (DIA 1032).

At the End of Phase 2 meeting, the sponsor submitted data from these studies, which it claimed as indication that both canagliflozin and metformin given alone met the standards for bioequivalence to the individual tablets given concurrently, for all dose strengths. However, the Agency communicated to the sponsor that as a whole, the bridging plan would not be acceptable because the PD markers that the sponsor had chosen for its Phase 1 studies (mean urinary excretion in 24 hours and 24-hour mean renal threshold for glucose excretion) had not been validated as surrogates for clinical efficacy in T2DM. At that time, the Agency instead recommended a head to head 16-20 week study to compare HbA1c change between QD vs BID dosing of canagliflozin.

The sponsor subsequently changed its bridging plan, which is reflected in this NDA submission, and includes two approaches: a bootstrap analysis to link results of separate QD and BID dosing studies, as well as a PK/PD and modeling and simulations approach.

**Figure 2: Sponsor's bridging plan included with NDA 204353**



Source: Dr. Ritesh Jain's Clinical Pharmacology Review

It is the position of the clinical pharmacology team that with respect to the PK/PD and modeling simulations approach above, study 1032 remains inadequate as a bridge because of the same concerns with the PD markers expressed at the End of Phase 2 meeting. Following a number of internal conversations between the clinical pharmacology and clinical teams regarding the sponsor's entire bridging program, there was agreement that the approach is not acceptable.

The sponsor, in a conference call with representatives of the Division of Metabolism and Endocrinology Products on October 31, 2013, attempted to provide further support for its bridging plan by referring to the modeling report previously submitted under NDA 204042. However, the clinical pharmacology team maintained that, based on the available concentration range, the PK/PD data submitted in NDA 204042 did not show a robust relationship between plasma canagliflozin concentrations and HbA1c response for canagliflozin. Dr. Jain's review has encapsulated the review team's thoughts from this meeting.

Subsequent to this communication, the sponsor submitted a revised PK/PD modeling plan, which was deemed by clinical pharmacology to have been submitted too late in the review cycle for adequate evaluation. Based on the issues with the sponsor's current bridging program stated above, the clinical pharmacology team has recommended a Complete Response.

- **Clinical Microbiology**

This submission does not contain new clinical microbiology data.

- **Clinical/Statistical- Efficacy**

As all the Phase 3 trials were previously reviewed in the canagliflozin NDA, see Dr.

Kwon's review of NDA 204042 for discussion of Phase 3 trials. Please also see Dr. Wei Liu's biostatistics review for further details.

In brief, the placebo-controlled Phase 3 trials primarily supporting the FDC (DIA3006, DIA3002, and DIA3012) had a core double-blind period with the primary endpoint at 26 weeks, and the DIA3008 Insulin Substudy/Population study had a core double-blind period of 18 weeks. In the 2 active-comparator, noninferiority trials (DIA3009 [versus glimepiride, background of metformin] and DIA3015 [versus sitagliptin, background of metformin and SU]), the primary endpoint was evaluated at 52 weeks.

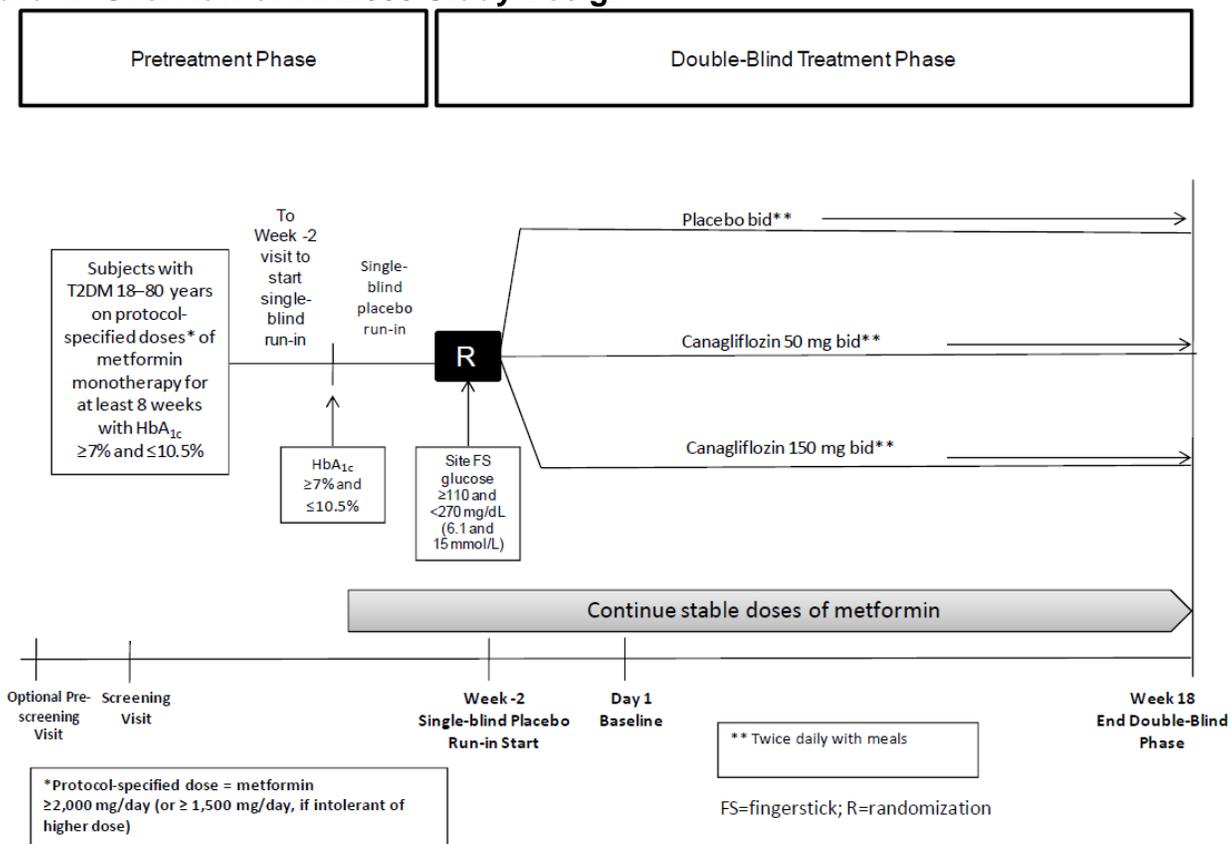
DIA2003 is summarized here, as this is a newly conducted Phase 2 trial in support of this FDC application. In addition, I have provided a brief synopsis of study DIA3006, one of the Phase 3 trials from the original canagliflozin NDA, as it was used as a comparator to DIA2003 to evaluate the glycemic efficacy of canagliflozin QD and BID at the same total daily doses.

### **DIA2003**

DIA2003 was an 18-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 2 trial evaluating the efficacy and safety of canagliflozin BID dosing in T2DM subjects with inadequate glycemic control on maximal or near maximal effective dose of metformin monotherapy ( $\geq 2000$  mg/day, or  $\geq 1500$  mg/day if unable to tolerate for at least 8 weeks). The primary objective of this trial was to demonstrate the superiority of canagliflozin 50 mg and 150 mg BID compared to placebo, as measured by the change in HbA1c from baseline to Week 18.

Eligible subjects were randomized in a 1:1:1 ratio to the addition of canagliflozin 50 mg BID, canagliflozin 150 mg BID, or matching placebo BID, to the ongoing stable dose of metformin monotherapy. Randomization was stratified by baseline HbA1c value ( $<$  or  $\geq 8\%$ ). After screening, eligible subjects entered a 2-week single-blind placebo run-in period before entering an 18-week, placebo-controlled, double-blind treatment period. Figure 1 shows an overview of DIA2003 study design.

**Figure 1: Overview of DIA2003 Study Design**



Source: CSR DIA2003, Figure 1

## Results

The primary efficacy endpoint in DIA2003 was the change in HbA<sub>1c</sub> from baseline at Week 18, using the LOCF approach. The placebo-adjusted LS mean change in HbA<sub>1c</sub> from baseline to Week 18 was -0.44% and -0.60% for canagliflozin 50 mg BID and 150 mg BID respectively, and reached statistical significance ( $p < 0.001$  for both comparisons). The results of sensitivity analyses such as PP analysis, completers' analysis, and MMRM were consistent and supported the primary analysis.

Secondary endpoints were also evaluated from baseline to Week 18 in DIA2003 and included changes in FPG, body weight, and proportion of subjects achieving HbA<sub>1c</sub> <7%. The LS mean change from baseline to Week 18 in FPG was statistically significant for both canagliflozin groups compared to the placebo group ( $p < 0.001$ ): the placebo-adjusted LS mean changes in FPG were -23.6 mg/dL and -24.0 mg/dL with canagliflozin 50 mg and 150 mg BID respectively. The placebo-subtracted proportion of subjects who achieve HbA<sub>1c</sub> <7% was about 16% with canagliflozin 50 mg BID and 26% with canagliflozin 150 mg BID.

## DIA3006

In order to evaluate the glycemic efficacy of canagliflozin QD and BID at the same total daily doses, the HbA<sub>1c</sub> reduction observed in DIA2003 was compared to DIA3006, a similarly designed Phase 3 trial evaluating canagliflozin QD as add-on to metformin.

The trial designs for DIA2003 and DIA3006 were similar with regard to study enrollment criteria, and the HbA1c criterion for study entry was 7 to 10.5% for both trials. However, the overall mean baseline HbA1c was lower in DIA2003 (7.6%) compared to DIA3006 (7.9%) despite similar inclusion criteria, and about 22.2% subjects had baseline HbA1c <7% in DIA2003 compared to 12.5% in DIA3006.

As previously described in the Clinical Pharmacology section, the magnitude of HbA1c reductions observed in DIA2003 with canagliflozin BID dosing was numerically smaller when compared to the same total daily dose of canagliflozin administered QD in DIA3006. To account for this baseline differences in HbA1c, the applicant conducted a simulation (i.e., bootstrap simulation) to demonstrate that the observed differences in HbA1c-lowering between these two trials were due to baseline differences in HbA1c.

One of the main study differences between these two trials was the duration of the double-blind treatment period (18 weeks in DIA2003 compared to 26 weeks in DIA3006). However, the HbA1c reductions at Week 18 in DIA3006 were numerically similar to Week 26 results, and the placebo-adjusted LS mean changes in HbA1c from baseline to Week 18 was -0.56% and -0.73% with canagliflozin 100 mg and 300 mg QD respectively. Therefore, the magnitude of HbA1c lowering in DIA2003 remains smaller than DIA3006 at the same time point (Week 18).

## • Safety

No new safety issues are noteworthy from the clinical pharmacology studies and the newly reviewed clinical trial DIA2003 submitted under this NDA. Please see Dr. Kwon's clinical review for a complete review of safety.

The safety data from a pooled dataset which included three placebo-controlled 26-week Phase 3 trials where canagliflozin was added to the background metformin therapy was reviewed and also compared to a similar pooled dataset of four placebo-controlled 26-week Phase 3 trials from the canagliflozin NDA. No additional safety concerns were identified with combined use of canagliflozin and metformin compared to the individual components. Canagliflozin was administered once daily in these Phase 3 trials, and in the FDC, the same total daily dose of canagliflozin is proposed to be administered twice daily due to the metformin component.

The newly conducted Phase 2 trial (DIA2003) for the FDC provided safety data for co-administration of canagliflozin twice daily with metformin IR. Particular safety issues germane to this review are listed below:

- One death was reported in study DIA2003 due to colon cancer in a subject who received canagliflozin 150 mg BID. Dr. Kwon and I reviewed this case and are in agreement that the latency of event (40 days) makes it unlikely to be causally related to canagliflozin treatment.
- Two nonfatal serious adverse events (SAEs) were reported. One involved a 58-year old woman with an indwelling urinary catheter who developed pyelonephritis and nephrolithiasis on Day 56 after starting canagliflozin 150 mg BID, leading to study discontinuation. Although canagliflozin has been associated with decreases in serum

urate levels, as well as nephrolithiasis, in my determination this particular case was not causally related to treatment. The second involved a 41-year old woman with a history of oroantral fistula who underwent a repair of the fistula developed a postoperative wound complication 35 days after study initiation. The event resolved on study day 52, and I do not believe this was related to canagliflozin treatment.

- In DIA2003, the largest incidence of adverse events leading to discontinuation was seen in the canagliflozin 150 mg BID group (7.5% [7 subjects]), and the most common event leading to discontinuation was vulvovaginal pruritus in two female subjects.
- No adverse events of myocardial infarction, stroke, hospitalized unstable angina, hospitalized congestive heart failure, venous thromboembolism, or fractures were reported. No volume depletion-related adverse events were reported. A higher incidence of subjects with osmotic diuresis-related events occurred in the canagliflozin 150 mg BID group (7.5% [7/93]) compared to none in canagliflozin 50 mg BID or placebo groups; these events were mild and none led to study discontinuation.

At the 4-month safety update, no new trends or patterns of deaths, SAEs, or adverse events leading to discontinuations were identified with canagliflozin.

In total, my review of study DIA2003 indicated a similar safety and tolerability profile of canagliflozin given alone to that of once daily administration of canagliflozin with metformin. Therefore, the safety and tolerability of co-administration of canagliflozin and metformin BID would be expected to be similar to its individual components.

- **Advisory Committee Meeting**

This application was not discussed before an advisory committee.

- **Pediatrics**

The proposed pediatric study plan was reviewed by the pediatric review committee on October 23, 2013. The pediatric review committee was in agreement with the study plan, which is the same as planned for the canagliflozin pediatric drug development plan and is outlined in Dr. Guettier's CDTL memo for NDA 204402.

- **Other Relevant Regulatory Issues**

None identified.

- **Labeling**

On April 26, 2013, the applicant submitted a labeling amendment to harmonize the labeling for the canagliflozin/metformin IR FDC with the final canagliflozin labeling approved on March 29, 2013.

- **Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

At the time of writing this CDTL memo, I recommend a Complete Response letter to the applicant.

This recommendation is based on inadequacies found in the sponsor's proposed plan to bridge the once- and twice daily canagliflozin doses, described fully in the Clinical Pharmacology section of this review. In brief, the sponsor has failed to demonstrate an exposure-response relationship for canagliflozin, as patients who receive canagliflozin QD appear to have superior clinical efficacy (measured in this program as change in HbA1c at 18 weeks of treatment) to those receiving the same daily dose BID. Furthermore, the PK/PD data submitted to the original canagliflozin NDA do not show a robust relationship between plasma canagliflozin concentrations and HbA1c response for canagliflozin. Finally, the sponsor's bioequivalence studies rely upon PD markers have not been validated as surrogates for clinical efficacy in T2DM.

- Risk Benefit Assessment

Pending resolution of the dose bridging issues, the risk benefit assessment for canagliflozin/metformin is otherwise favorable.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management will be required.

- Recommendation for other Postmarketing Requirements and Commitments

The requirement for PREA-related PMRs is discussed in Section 10 of this memo.

- Recommended Comments to Applicant

At the time of this CDTL review, a CR letter is being drafted and comments will be forthcoming.

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/s/  
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ALI MOHAMADI  
12/10/2013

JEAN-MARC P GUETTIER  
12/10/2013

I agree with Dr. Mohamadi's assessment

## Summary Review for Regulatory Action

<b>Date</b>	11/30/2013
<b>From</b>	Jean-Marc Guettier
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	204353
<b>Supplement #</b>	
<b>Applicant Name</b>	Janssen Research and Development, LLC.
<b>Date of Submission</b>	December 12, 2012
<b>PDUFA Goal Date</b>	December 12, 2013
<b>Proprietary Name / Established (USAN) Name</b>	(b) (4) (canagliflozin/metformin HCl)
<b>Dosage Forms / Strength</b>	Tablets Canagliflozin 50 mg/metformin 500 mg Canagliflozin 50 mg/ metformin 1000 mg Canagliflozin 150 mg/metformin 500 mg Canagliflozin 150 mg/metformin 1000 mg
<b>Proposed Indication(s)</b>	1. As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets
<b>Action/Recommended Action for NME:</b>	<i>Complete Response</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Kwon Hyon, PharmD
Statistical Review	Wei Liu, PhD
Pharmacology Toxicology Review	Fred Alavi, PhD
CMC Review/OBP Review	Sheldon Markofsky PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Ritesh Jain, PhD
DDMAC	N/A
DSI	N/A
CDTL Review	Ali Mohamadi, MD

OND=Office of New Drugs  
 DDMAC=Division of Drug Marketing, Advertising and Communication  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DSI=Division of Scientific Investigations  
 DDRE= Division of Drug Risk Evaluation  
 DRISK=Division of Risk Management  
 CDTL=Cross-Discipline Team Leader

## 1. Introduction

On December 12<sup>th</sup> 2012, Janssen submitted a new drug application for the fixed dose combination product canagliflozin and metformin hydrochloride under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act.

The product is a fixed dose combination (FDC) of canagliflozin and metformin hydrochloride. The dosage form is a film-coated, immediate release, tablet and the route of administration is oral. The dosage strengths are 50mg/500mg, 50mg/1000mg, 150mg/500mg and 150mg/1000mg for canagliflozin and metformin hydrochloride respectively.

The daily dosing frequency of canagliflozin in the FDC product differs from the dosing frequency of the single entity canagliflozin product (NDA# 204042) in that it is administered twice instead of once daily. The dosing frequency of metformin hydrochloride in the FDC product is the same as the dosing frequency of the single entity metformin hydrochloride product (NDA# 20357).

The proposed indication for the FDC product is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM who are not adequately controlled on a regimen containing metformin or canagliflozin, or in patients who are already treated with both canagliflozin and metformin.

The applicant relies on the Agency's previous finding of safety and efficacy by referencing NDA# 204042 (Canagliflozin single product, approved March 29th 2013) and NDA# 20357 (metformin hydrochloride single product, approved in 1995) to support approval of the fixed dose combination product.

## 2. Background

The applicant references trials in NDA# 204042 (Canagliflozin single product, approved March 29th 2013) to support approval of the fixed dose combination product. These trials demonstrated that addition of canagliflozin to a stable maximally effective dose of metformin improves glycemic control in subjects with type 2 diabetes inadequately controlled at baseline.

A major difference between NDA# 204042 and the current application is that in pivotal trials included in NDA# 204042 the full daily dose of canagliflozin was delivered as a single administration **once daily**. In the FDC product NDA however, the full daily dose of canagliflozin is split in half and delivered in two administrations **twice daily**. To justify appropriateness of reliance on data from NDA# 204042 to support approval of the FDC product, the applicant needed to convincingly demonstrate that the difference in administration schedules would not impact efficacy and safety. One way to bridge the

efficacy and safety findings in the two applications was through a comparative bioavailability study. The appropriateness of the efficacy bridge in this scenario is dependent on having first established a robust relationship between steady state canagliflozin plasma exposure and HbA1c response. An alternate approach would be to compare head to head, within a single trial, the efficacy achieved when the daily dose of canagliflozin is delivered once daily to the efficacy achieved when the daily dose is split and delivered in two administrations.

The applicant demonstrated that overall exposure (AUC) to canagliflozin at steady state is similar whether the daily canagliflozin dose is delivered as a full dose once daily or as two half doses twice daily. Differences in  $C_{max}$  were expected and noted. The applicant however, did not establish a robust relationship between canagliflozin plasma levels and HbA1c response. The applicant submitted a phase 2 trial (DIA2003) comparing the glucose lowering effect of the FDC product to placebo at 18 weeks. In this trial however, the applicant did not directly compare the HbA1c response achieved when canagliflozin is delivered as a single dose once daily to the HbA1c response achieved when an equivalent dose of canagliflozin is split and delivered in two administrations twice daily.

Absent a clear plasma canagliflozin exposure-HbA1c response relationship or a within trial head to head comparison establishing similarity in efficacy between the two canagliflozin dosing regimens, it is not appropriate to rely on the Agency's previous finding of safety and efficacy from NDA# 204042 to support approval of the fixed dose combination product.

Drs. Mohamadi and Jain have reviewed the regulatory history of the application and the reader is referred to their reviews for details.

### **3. CMC/Device**

Chemistry, manufacturing and controls data related to the drug substance manufacturing process were found to be acceptable and are detailed in Dr. Sheldon Markofsky's review. The biopharmaceutics reviewer, Dr. Okponanabofa Eradiri, reviewed the dissolution method and dissolution specifications to be used for registration, batch release and stability testing and found them to be acceptable for approval.

### **4. Nonclinical Pharmacology/Toxicology**

The pharmacology and toxicology of canagliflozin has been fully reviewed under NDA# 204042. The pharmacology and toxicology of metformin hydrochloride has been fully reviewed under NDA# 20357. In support of co-administration the applicant submitted a 3 month combination GLP toxicology study (#TOX9667) and an embryo-fetal development GLP toxicology study (#TOX9590) in rats.

The combination toxicology study revealed that metformin co-administration neither impacted canagliflozin exposure or its toxicity profile. The findings of glycosuria, polyuria,

weight loss, renal tubule dilatation, renal pelvis dilatation and trabecular bone hyperostosis were consistent with canagliflozin's known toxicology profile. In the combination toxicology study, mid and high doses of canagliflozin were observed to increase metformin's overall exposure (AUC) by 1.4 to 1.8-fold, an effect attributed to decreased renal perfusion secondary to canagliflozin-induced hemodynamic changes.

The embryo-fetal study showed that addition of metformin to canagliflozin did not have a meaningful impact on canagliflozin induced maternal and embryo-fetal developmental changes in rat.

## 5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology data are pivotal in this application and are detailed in Drs. Jain and Mohamadi's reviews. The following briefly summarizes the major findings. Please refer to their reviews for full details.

### **Efficacy and safety of canagliflozin co-administered with metformin at maximally effective dose**

The applicant relies on the Agency's previous finding of safety and efficacy from NDA# 204042 (Canagliflozin single product, approved March 29th 2013) to support approval of the fixed dose combination product. The applicant leverages several "add-on" to metformin trials (reviewed in Section 7 below) from this NDA. One major difference between NDA# 204042 and the current application is that in NDA# 204042 the daily dose of canagliflozin was administered once daily (e.g., 100 mg QD). For the FDC product however, the daily dose is to be administered in divided doses twice daily (e.g., 50 mg BID). The applicant attempts to bridge once to twice daily administration using a complicated scheme described in Drs. Jain's and Mohamadi's reviews and summarized below. The bridging strategy and deficiencies identified by the clinical pharmacology reviewers and summarized in Dr. Mohamadi's review are italicized.

#### **A. Bridging Strategy between once and twice daily canagliflozin dosing**

- 1. Steady State Bioavailability (Trial# DIA1032):** Steady-state PK (i.e.,  $C_{max}$ ,  $AUC_{24hrs}$ ) and PD [Urinary Glucose Excretion/Renal Threshold for Glucose Excretion (UGE/RTG)] comparisons between twice daily administered canagliflozin versus once daily administered canagliflozin (note: not added to metformin) are provided in this study.

***Deficiency: A robust relationship between PD markers used in this study (UGE/RTG) and HbA1c reduction is not established. Absent this relationship, UGE cannot be used as a surrogate to predict long-term HbA1c response. This study is not sufficient to bridge efficacy (i.e., based on HbA1c) between once and twice daily dosing.***

**2. Population PK/PD modeling submitted in NDA# 204042:**

**Deficiency:** *A robust relationship between plasma canagliflozin concentrations and HbA1c response was not established. Assumptions used for population PK/PD modeling were not entirely justified (i.e., limited available concentration range, model was built on average plasma concentration and not on the full drug concentration profile). The pharmacometric team asked that these be clarified through several information requests. Specific areas of disagreement between the sponsor and Agency related to population PK/PD modeling are summarized in Dr. Jain's review.*

- 3. Bootstrap analysis:** An attempt to reconcile observed efficacy differences between two "similarly" designed clinical trials [i.e., **DIA3006** (canagliflozin once daily added to max effective metformin dose) and **DIA2003** (canagliflozin twice daily added to max effective metformin)].

**Deficiency:** *This analysis was post-hoc and cannot be used to overcome deficiencies 1 and 2.* (Summarized in Section 7 of this memorandum)

**B. Bridge between the to-be-marketed FDC product formulation and formulations used in pivotal trials DIA1032 and DIA2003:**

The FDC product was not used in pivotal trials. In these trials, canagliflozin and metformin (only for DIA2003) were administered separately and not as a single tablet. To link the to-be-marketed product to the products used in pivotal trials, single dose relative bioavailability studies for each of the dosage strengths proposed were carried out. In these studies the to-be-marketed FDC product was compared to individually co-administered products. It is important to note that these studies do not compare twice daily administration to once daily administration since the entire daily dose of the FDC product (i.e., two tablets) was taken at one sitting and was compared to equivalent doses of the two products taken individually also at one sitting. In the studies listed below, the plasma concentration time curves for canagliflozin and metformin were found to meet bioequivalence criteria (i.e., based on geometric mean comparisons for  $C_{max}$ ,  $AUC_{last}$  and  $AUC_{\infty}$  comparisons) whether administered as a FDC product or as co-administered, separate, individual products.

- **DIA1046**
  - Compared two tablets of FDC (50/500 mg) to one tablet of canagliflozin (100 mg) and two tablets of metformin (500 mg)
- **DIA1051**
  - Compared two tablets of FDC (50/1000 mg) to one tablet of canagliflozin (100 mg) and two tablets of metformin (1000 mg)
- **DIA1050**
  - Compared two tablets of FDC (150/500 mg) to one tablet of canagliflozin (300 mg) and two tablets of metformin (500 mg)

- **DIA1038**
  - Compared two tablets of FDC (150/1000 mg) to one tablet of canagliflozin (300 mg) and two tablets of metformin (1000 mg)

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical-Efficacy

The applicant relies on the Agency's previous finding of safety and efficacy from NDA# 204042 (Canagliflozin single product, approved March 29th 2013) to support approval of the fixed dose combination product. Specific clinical trials that support the safety and efficacy of canagliflozin once daily co-administered with metformin twice daily at maximally effective doses and previously reviewed in NDA# 204042 were:

### Add-on to Metformin Trials

- **DIA3006 - 26 week trial**
  - Compared once daily canagliflozin (100 and 300 mg) to placebo
  - This trial had a double blind 26-week active controlled (sitagliptin 100 mg) extension
- **DIA3009 - 52 week trial**
  - Compared once daily canagliflozin (100 and 300 mg) to maximum tolerated glimepiride dose (i.e., up to 6-8 mg according to country specific label)
  - This trial had a double blind 26-week extension

### Add-on to Metformin and another anti-diabetic agent

- **DIA3002: add on to metformin and sulfonylurea - 26 week trial**
  - Compared canagliflozin once daily (100 and 300 mg) to placebo
  - This trial had a double blind 26-week placebo controlled extension
- **DIA3012: add on to metformin and pioglitazone - 26 week trial**
  - Compared canagliflozin once daily (100 and 300 mg) to placebo
  - This trial had a double blind 26-week controlled extension (sitagliptin 100 mg)
- **DIA3015: add on to metformin and sulfonylurea - 52 week trial**
  - Compared canagliflozin once daily (100 and 300 mg) to sitagliptin (100 mg)

In this application Janssen submits a new 18-week, randomized, double-blind, placebo-controlled, multicenter Phase 2 study (**DIA2003**) evaluating the efficacy and safety of canagliflozin administered twice daily in adult patients (i.e.,  $\geq 18$  and  $\leq 80$  years of age) with T2DM inadequately controlled (i.e., HbA1c 7.5-10.5%) on maximally effective doses of

metformin (i.e.,  $\geq 2000$  mg/day, or  $\geq 1500$  mg/day if unable to tolerate) for at least 8 weeks prior to the screening visit.

Subjects who met screening criteria and were eligible, entered a 2-week single blind placebo run-in period and were randomly assigned to receive either canagliflozin 50 mg, canagliflozin 150 mg or matching placebo twice daily with meals for 18-weeks in a 1:1:1 fashion. Randomization was stratified by baseline HbA1c (i.e.,  $<$  or  $\geq 8\%$ ).

The primary objective of the trial was to assess the superiority of canagliflozin 150 mg administered twice daily on HbA1c compared to placebo. The first of the secondary objectives was to assess the superiority of canagliflozin 50 mg administered twice daily on HbA1c compared to placebo.

The primary endpoint was the change in HbA1c from baseline to Week 18. The LOCF method was used to impute missing 18-week data. The primary analysis model was an ANCOVA model that used treatment and randomization strata as fixed factors and baseline HbA1c as a covariate. Analyses were based on the modified intent-to-treat population (mITT). The mITT included all subjects randomly assigned to a treatment group who had received at least 1 dose of study drug and had both a baseline and post-baseline HbA1c value. Type-1 error for secondary endpoints was controlled using a procedure that involved a pre-specified endpoint hierarchy. The results of the primary and first secondary analyses for DIA2003 are shown in the table.

**Table 1: Efficacy DIA2003 in mITT population using LOCF.**

Treatment Arm	n	Mean Baseline HbA1c (SD)	Adjusted Mean HbA1c Change From Baseline (SE)	Adjusted LS Mean Between Group Difference in HbA1c [ (95% CI)	p-value
Placebo	92	7.66 (0.91)	-0.01 (0.07)		
Cana 50 <b>BID</b>	90	7.63 (0.84)	-0.45 (0.07)	<b>-0.44 (-0.64, -0.25)</b>	<b>&lt;0.0001</b>
Cana 150 <b>BID</b>	91	7.53 (0.83)	-0.61 (0.069)	<b>-0.60 (-0.79, -0.41)</b>	<b>&lt;0.0001</b>
Estimates are based on an ANCOVA model adjusting for treatment, HbA1c strata, and baseline HbA1c.					

Canagliflozin administered **once daily** was not a comparator in **DIA2003**. This would have allowed a within trial, randomized, comparison of the effect of once versus twice daily canagliflozin administration on the change in HbA1c from baseline.

To demonstrate that twice daily dosing had similar glycemic efficacy as once daily dosing the applicant bridged the HbA1c reduction between twice and once daily dosing using a cross study comparison (i.e., **DIA2003** versus **DIA3006** in NDA 204042). **DIA3006** had similar enrollment criteria to **DIA2003**. The magnitude of the HbA1c reduction from baseline to 18-weeks, for each of the two doses of canagliflozin, was observed to be numerically larger when canagliflozin was administered once daily (See Table 3 below). The disparate glycemic

efficacy results between **DIA2003** and **DIA3006** could have arisen due to between trial differences in a number of factors (some not readily quantifiable) or could have occurred due to pharmacodynamic differences between canagliflozin administered once (e.g., > intestinal SGLT-1 inhibition) versus twice daily.

**Table 3: Change in HbA1c from baseline at 18 Weeks in DIA3006.**

Treatment Arm	n	Mean Baseline HbA1c (SD)	Adjusted Mean HbA1c Change From Baseline (SE)	Adjusted LS Mean Difference in HbA1c [ (95% CI)	p-value
Placebo	92	7.94 (0.93)	-0.22 (0.07)		
Cana 100 <b>QD</b>	90	7.87 (0.86)	-0.82 (0.05)	<b>-0.59 (-0.75, -0.43)</b>	<b>&lt;0.0001</b>
Cana 300 <b>QD</b>	91	7.85 (0.90)	-0.90 (0.08)	<b>-0.67 (-0.83, -0.51)</b>	<b>&lt;0.0001</b>

mITT population at 18-weeks using LOCF Estimates are based on an ANCOVA model adjusting for treatment, HbA1c strata, and baseline HbA1c.

The applicant believes that the lower efficacy observed in DIA2003 when canagliflozin was administered twice daily is due to cross trial differences in baseline HbA1c and not due to differences in pharmacodynamics. To reconcile differences in efficacy between the two studies the applicant conducted a simulation study using a bootstrap procedure. This simulation assessed the potential impact of baseline glycemic control on the primary efficacy analysis between the two studies.

Drs. Liu and Sahlroot noted at the mid-cycle meeting that the information gained from this type of approach is exploratory and is not robust enough to support a regulatory decision. Interpretation of the results in these types of analyses are severely limited due to their post-hoc nature, their reliance on non-randomized, single arm, cross trial comparisons and due to the fact that the model adjusts for only one of the many potential differences between the two studies (i.e., baseline glycemic control). Dr. Liu concludes that a simulation (i.e., bootstrap procedure) is not a substitute for a PK/PD bridge.

## 8. Safety

This has been reviewed in Drs. Kwon and Mohamadi’s review. No new safety issues were identified in this application.

## 9. Advisory Committee Meeting

No efficacy or safety issues requiring the input from an advisory panel was needed for this application. Therefore no advisory committee was convened.

## 10. Pediatrics

Not applicable at this time due to recommended complete response action

## **11. Other Relevant Regulatory Issues**

No other relevant regulatory issues were identified.

## **12. Labeling**

Not applicable at this time due to a recommended complete response action.

## **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

I recommend a complete response.

- Risk Benefit Assessment

The risk and benefit of the FDC products were not directly established in the application. The applicant is fully reliant on data from NDA#204042 to inform the benefit risk of the FDC product. To justify such reliance, the applicant had to convincingly demonstrate that benefit risk data from NDA# 204042 informed the benefit risk of the FDC product by creating an appropriate scientific bridge between the two applications. For the reasons I have detailed in Sections 5 and 7 an appropriate scientific bridge between the two applications is lacking.

Comparing results from DIA2003 to DIA3006 leaves open the possibility that administering canagliflozin in the form of a fixed dose combination reduces the efficacy of the product. If this is the case, the benefit derived from addition of canagliflozin to a patient inadequately controlled on metformin would differ depending on which of the canagliflozin product is used. In such a scenario a patient administered the FDC form for convenience would stand to benefit less. Furthermore, a patient controlled on both products individually may experience worsening glycemic control if switched to the FDC products for convenience.

The applicant will be asked to establish a clear and robust canagliflozin plasma exposure to HbA1c relationship with the data they have on hand but that were not included in the application. If the applicant cannot establish this relationship, they will need to design an adequate and well controlled trial to compare the difference in the change in HbA1c from baseline when canagliflozin is administered as a 100 mg once daily dose versus a 50 mg twice daily dose in patients with type 2 DM inadequately controlled on metformin.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable at this time due to recommended complete response action.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable at this time due to recommended complete response action.

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/s/  
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JEAN-MARC P GUETTIER  
12/10/2013

## CLINICAL REVIEW

Application Type 505(b)(2)  
Application Number(s) 204353  
Priority or Standard Standard

Submit Date(s) December 12, 2012  
Received Date(s) December 12, 2012  
PDUFA Goal Date December 12, 2013  
Division / Office DMEP/ODE 2

Reviewer Name(s) Hyon J Kwon, PharmD, MPH  
Review Completion Date October 31, 2013

Established Name Canagliflozin/metformin HCL  
(Proposed) Trade Name (b) (4)  
Therapeutic Class SGLT2 inhibitor and biguanide  
Applicant Janssen Research and  
Development, LLC

Formulation(s) Canagliflozin/metformin HCL  
IR FDC tablets at dosages of  
50/500, 50/1000, 150/500, and  
150/1000 mg  
Dosing Regimen Twice daily  
Indication(s) As an adjunct to diet and  
exercise to improve glycemic  
control in adults with type 2  
diabetes mellitus who are not

adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets

Intended Population(s) Type 2 diabetes mellitus

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

Unless the Clinical Pharmacology Review recommends approval based on adequate clinical pharmacology data for bridging the once-daily dosing of canagliflozin to the proposed twice-daily dosing for the fixed dose combination, I do not recommend approval of the canagliflozin/metformin immediate release fixed dose combination for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets. The final review from Clinical Pharmacologist is pending at the time of this review. See section 1.2 for my rationale.

### 1.2 Risk Benefit Assessment

Canagliflozin (Invokana, NDA 204-042) was approved for the treatment of T2DM in the US on March 29, 2013, and approved doses are 100 mg and 300 mg once daily (QD). Metformin (Glucophage, NDA 020-357) was approved for the treatment of T2DM on March 3, 1995. The applicant submitted a 505(b)(2) NDA for the following canagliflozin/metformin immediate release (IR) fixed dose combination (FDC) tablet strengths, with Glucophage as the reference listed drug: 50/500 mg, 50/1000 mg, 150/500 mg, and 150/1000 mg to be given twice daily.

The applicant has conducted a typical development program for an anti-diabetic FDC tablet including a CMC package, a bridging toxicology study, pivotal bioequivalence studies showing that the FDC is bioequivalent to co-administered components at equal doses, and supportive Phase 3 trials with co-administration of individual components. The applicant also conducted a food effect study to support administration of the FDC with meals.

The critical issue for this FDC approval is bridging the single-agent canagliflozin program to the FDC because of dosing differences between the two products. The efficacy and safety of canagliflozin was well-established with once daily (QD) administration of 100 mg and 300 mg in the Phase 3 program. Due to the posology of metformin IR component, the FDC is proposed to be dosed twice daily (BID), and thus the canagliflozin component will be divided to provide the same total daily dose (i.e., 50 mg and 150 mg BID).

At the time of the Late-Cycle Meeting, the Agency's Clinical Pharmacologists concluded that the exposure-response relationship for plasma canagliflozin and HbA1c response

was not well supported, and the Pharmacokinetic (PK)/Pharmacodynamic (PD) model submitted in this NDA was inadequate to bridge the QD and BID dosing regimen as the PD marker was not validated as a surrogate for efficacy. Subsequent to the Late-Cycle Meeting, the applicant submitted a new PK/PD analysis plan, but the Clinical Pharmacologists do not believe that their proposed plan would be adequate to bridge the efficacy of QD and BID dosing regimen due to limitations of the available data. The final review from Clinical Pharmacology is pending at this time.

With regard to the clinical data, a new Phase 2 trial, DIA2003, was conducted to support the BID dosing of canagliflozin with the FDC. DIA2003 was an 18-week trial evaluating the efficacy and safety of canagliflozin BID dosing (50 mg and 150 mg BID) compared to placebo. Because this trial did not have a comparative canagliflozin QD dosing arm, the glycemic efficacy results of DIA2003 were compared to DIA3006, a similarly designed Phase 3 trial evaluating canagliflozin QD as add-on to metformin.

Comparison of DIA2003 and DIA3006 showed that the magnitude of HbA1c reduction in DIA2003, where canagliflozin was administered BID, was smaller than that observed in DIA3006, where the same total daily doses of canagliflozin were administered QD. In DIA2003, the placebo-adjusted LS mean changes in HbA1c from baseline to Week 18 were -0.44% and -0.60% for canagliflozin 50 mg BID and 150 mg BID respectively. In DIA3006, the placebo-adjusted LS mean changes in HbA1c from baseline to Week 26 were -0.62% and -0.77% for canagliflozin 100 mg QD and 300 mg QD respectively. The HbA1c reductions at Week 18 were similar to Week 26 in DIA3006, and thus the difference in duration of treatment period between two trials did not appear to be a factor that led to difference in efficacy.

The applicant noted that the baseline HbA1c was lower in DIA2003 (7.6%) compared to DIA3006 (7.9%) despite similar HbA1c inclusion criterion for enrollment (7 to 10.5%). The applicant used a bootstrap method to demonstrate that the difference in efficacy observed between the two trials was due to baseline differences in HbA1c. However, as discussed by our Statistical Reviewer, cross trial comparison is difficult to interpret, and a post-hoc analysis to account for one prognostic factor between two trials is not conclusive as it does not account for other known or unknown prognostic factors. Therefore, in the absence of an exposure-response relationship for plasma canagliflozin concentrations and HbA1c response, the clinical data is inadequate to bridge the efficacy of QD data from the canagliflozin NDA to the proposed BID dosing regimen for the FDC.

 (b) (4)  
However, without any data to support that BID dosing would lead to similar glycemic control as QD dosing at the same total daily doses of canagliflozin, I do not recommend the approval of FDC. Patients who are already on both canagliflozin and metformin dosed as separate tablets may switch to FDC for

convenience if it becomes available, and based on the clinical evidence submitted in this NDA, these patients would potentially lose their glycemic control by switching to FDC.

Based on my review of safety data, I did not identify any safety concerns that would preclude the combined use of canagliflozin with metformin, either as QD or BID dosing.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No new safety concerns were identified that prompt the need for Risk Evaluation and Mitigation Strategies with canagliflozin/metformin IR FDC.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

Several postmarketing studies are required under canagliflozin (NDA 204-042), and I do not recommend any new postmarketing requirements or commitments for the canagliflozin/metformin IR FDC. The required pediatric assessments under the Pediatric Research Equity Act (PREA) for canagliflozin/metformin IR FDC can be met by fulfilling the required PREA studies under canagliflozin NDA, with the addition of a swallowability study with the FDC tablet.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

The applicant submitted a 505(b)(2) NDA for approval of canagliflozin as a FDC with metformin HCl IR, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

The applicant referenced information from the canagliflozin NDA (204-042) and from the Glucophage NDA (020-357).

Canagliflozin is an orally active, competitive, reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2). Inhibition of SGLT2 reduces renal reabsorption of filtered glucose and increases urinary glucose excretion, thereby lowering plasma glucose levels in patients with T2DM. Unlike most other approved non-insulin anti-diabetic drugs currently indicated for the treatment of T2DM, the direct glucose lowering effect of canagliflozin does not depend on augmenting endogenous insulin secretion or

improving insulin sensitivity. Its effect is dependent on the ability to excrete glucose in the urine, which is correlated to both plasma glucose levels and glomerular filtration rate (GFR), and thus the glucose lowering effect of canagliflozin is expected to decline with decreasing renal function. It was approved for the treatment of T2DM in the US on March 29, 2013 (NDA 204-402).

Metformin is an oral biguanide, which decreases production of hepatic glucose and intestinal absorption of glucose, and improves insulin sensitivity. It was approved for the treatment of T2DM in US as Glucophage on March 3, 1995 (NDA 020-357).

The applicant proposes to market 50/500 mg, 50/1000 mg, 150/500 mg, 150/1000 mg of canagliflozin/metformin FDC, to be given twice daily (BID) with meals. It should be noted that canagliflozin is recommended to be taken before the first meal of the day, at a once daily (QD) dose of 100 mg and 300 mg. The posology of FDC is proposed as BID administration because of metformin IR component which is given twice daily, and also with meals because metformin is recommended to be taken with meals to reduce the gastrointestinal side effects.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and the following drug therapies, either alone or in combination:

- Biguanides: metformin (e.g., Glucophage)
- Sulfonylureas: glyburide (Micronase), glipizide (Glucotrol), glimepiride (Amaryl), chlorpropamide (Diabinese), tolazamide (Tolinase)
- Insulin
- GLP-1 agonist: exenatide (Byetta), liraglutide (Victoza)
- Thiazolidinediones (TZDs): rosiglitazone (Avandia), pioglitazone (Actos)
- Dipeptidyl peptidase 4 (DPP-4) inhibitor: sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina)
- Meglitinides: repaglinide (Prandin), nateglinide (Starlix)
- $\alpha$ -Glucosidase inhibitor: acarbose (Precose), miglitol (Glyset)
- Pramlintide (Symlin)
- Dopamine agonist: bromocriptine mesylate (Cycloset)
- Bile acid sequestrants: colesevelam (WelChol)
- Various fixed dose combinations of oral therapies (e.g., Janumet, ActoPlus Met, Kombiglyze XR, Oseni, Kazano)

## 2.3 Availability of Proposed Active Ingredient in the United States

Canagliflozin (NDA 204-402) and metformin (Glucophage, NDA 020-357) have been approved for the treatment of T2DM in the US since March 29, 2013 and March 3, 1995, respectively.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Labeled safety concerns with canagliflozin include the following:

- Contraindicated in patients with severe renal impairment (estimated GFR <30 mL/min/1.73m<sup>2</sup>), end-stage-renal disease, or on dialysis;
- Hypotension: the risk is increased in patients with renal impairment, elderly, low systolic blood pressure, or if on diuretics, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB);
- Impairment in renal function;
- Hyperkalemia: the risk is increased in patients with moderate renal impairment taking drugs that interfere with potassium excretion or ACEI or ARB;
- Hypoglycemia with concomitant use with insulin or insulin secretagogue;
- Genital mycotic infections;
- Hypersensitivity reaction;
- Increased LDL-C;
- Urinary tract infections.

Labeled safety concerns with metformin include the following:

- Lactic acidosis: the risk increases with sepsis, dehydration, excessive alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure;
- Contraindicated in patients with renal impairment (e.g., serum creatinine  $\geq 1.5$  mg/dL for males,  $\geq 1.4$  mg/dL for females, or abnormal creatinine clearance);
- Potential for acute alteration of renal function when undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures requiring restricted intake of food and fluids;
- Decrease in Vitamin B12 levels;
- Hypersensitivity;
- Hypoglycemia, in elderly and debilitated patients when calorie intake is deficient, or during concomitant use with other glucose-lowering agents (such as sulfonyleureas and insulin).

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Preliminary discussions for the canagliflozin/metformin FDC program occurred at an EOP2 (April 28, 2009) and pre-NDA meeting (April 13, 2012) for the single-agent canagliflozin program. Interactions specific for the FDC program occurred at the EOP2 meeting on August 30, 2010, and pre-NDA meeting questions and additional interactions on August 30 and September 7, and 11, 2012.

At the EOP2 meeting for the FDC program on August 30, 2010, there were discussions related to bridging the safety and efficacy from the once-daily canagliflozin dosing regimen used in the Phase 3 program to the proposed twice-daily dosing with

canagliflozin/metformin IR FDC. The applicant proposed a Phase 1 PK/PD study comparing canagliflozin BID to QD for bridging, and we stated that this would be insufficient unless a robust exposure-response relationship is established for plasma canagliflozin concentration and HbA1c response for canagliflozin, as the PD marker was not validated as a surrogate for efficacy. We recommended that the applicant conduct an efficacy/safety clinical study to support the BID dosing of canagliflozin. During the meeting, the applicant commented that they planned to evaluate the relationship between the PD markers (renal glucose threshold parameters) and HbA1c to develop a robust model where their proposed PD markers may meet the FDA definition of a “well-established” surrogate for efficacy. The applicant suggested a Phase 2 trial of 60-80 subjects for 12 weeks to compare QD versus BID dosing, and we recommended that the trial be at least 16-20 weeks in duration with enough power to demonstrate an effect. As a post-meeting comment/question, the applicant described a 16-week, 3-arm study with 60-80 patients per arm in T2DM patients, with 2 doses of canagliflozin (50 mg and 150 mg BID) adequately powered to establish HbA1c-lowering relative to placebo. The Division concurred that this was an acceptable design in lieu of the proposed Phase 1 PK/PD study.

**Reviewer’s comment: We gave concurrence that their proposed Phase 2 trial would be acceptable in lieu of a Phase 1 PK/PD study comparing canagliflozin BID to QD, and the applicant has conducted a Phase 2 trial (DIA2003) in support of this FDC following the EOP2 discussion. Based on the preceding discussions during the meeting, this was acceptable since the applicant also planned to develop a robust model to establish a relationship between the PD markers and HbA1c.**

During the pre-NDA meeting questions and interactions, the following key clinical points were conveyed:

- Submission to include summaries and discussions relevant to the efficacy and safety of the combination therapy of canagliflozin plus metformin, and also include complete study reports of any individual studies not previously submitted to the canagliflozin NDA that support the marketing of FDC product;
- Agreed that the applicant can cross-reference clinical information that is already presented in the canagliflozin NDA;
- Submission to include a summary of pooled Phase 3 placebo-controlled studies where canagliflozin was added to metformin, and to highlight any differences observed from the overall pool of Phase 3 placebo-controlled trials in the canagliflozin NDA.

## 2.6 Other Relevant Background Information

On May 29, 2013, a Mid-Cycle Teleconference occurred with the applicant, and a Mid-Cycle Communication letter was issued on June 6, 2013. The following were significant issues that were communicated to the applicant:

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

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

Also, I requested narratives for any additional subjects with adjudicated hepatic events, bladder, breast, and renal cancer events as of the 4-Month Safety Update. The applicant submitted these narratives on June 28, 2013.

On September 12, 2013, a Late-Cycle Meeting (LCM) occurred with the applicant. The following are substantive review issues that were communicated and discussed during the LCM, which involved bridging glycemic efficacy from QD dosing in the canagliflozin program to the BID dosing for the canagliflozin/metformin FDC (see the Late-Cycle Meeting Minutes finalized on September 26, 2013 for full details):

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

Clinical: As discussed during the mid-cycle teleconference and written communication dated June 6, 2013, the magnitude of the HbA1c reduction observed at 18-weeks in Study DIA2003 (i.e., - 0.4% for 50 mg BID dose), when canagliflozin is administered twice daily, was numerically smaller than the HbA1c reduction observed at 26-weeks in Study DIA3006 (i.e., -0.6% for the 100 mg QD dose), when canagliflozin is administered once daily (Study DIA3006). You have attempted to bridge differences in observed efficacy across the two studies using post-hoc analyses which were not pre-specified. Post-hoc comparisons of

efficacy across clinical studies have several limitations and can be confounded by many known and unknown factors. In the absence of a well-established plasma canagliflozin exposure HbA1c response relationship, the clinical data submitted in NDA 204353 is not adequate to bridge the efficacy.

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

In response to LCM discussions, the applicant submitted a new PK/PD analysis plan on October 15, 2013 to compare the effect of QD and BID canagliflozin dosing on glycemic efficacy (i.e., HbA1c reduction). At the time of this review, the Clinical Pharmacologists do not believe that their proposed plan would be adequate to bridge the efficacy of QD and BID dosing regimen due to limitations of the available data.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

The quality of submission was acceptable. The submission was organized and information was not difficult to find.

#### **3.2 Compliance with Good Clinical Practices**

The applicant stated that the clinical development program presented in support of the canagliflozin/metformin IR FDC was conducted in full compliance with International Conference on Harmonization Good Clinical Practice guidelines.

The Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations, inspected the clinical and analytical data generated from the pharmacokinetic and bioequivalence studies, DIA1032 and DIA1038, and found them acceptable. No other inspections were requested for this FDC.

#### **3.3 Financial Disclosures**

FDA Form 3454 was submitted by the applicant. The only new studies submitted under the FDC NDA were seven Phase 1 trials (DIA1036, DIA1037, DIA1038, DIA1046, DIA1047, DIA1050, and DIA1051) and one Phase 2 trial (DIA2003). Financial

disclosures for all other trials were reviewed in the canagliflozin NDA and found to be acceptable.

Two investigators who participated in DIA2003 submitted FDA Form 3455 with the following financial disclosures:

- [REDACTED] <sup>(b) (6)</sup>, a Principal Investigator, reported a significant equity interest in Johnson & Johnson in excess of \$50,000;
- [REDACTED] <sup>(b) (6)</sup>, a Sub-Investigator, reported receiving compensation in the forms of honoraria and consulting fees in excess of \$25,000 from the applicant during the course of DIA2003 trial.

Any potential bias from these investigators will have minimal, if any, effect on the efficacy and safety conclusions since DIA2003 was a randomized, double-blind, placebo-controlled multicenter trial, and these investigators enrolled a small fraction of 279 enrolled subjects [REDACTED] <sup>(b) (6)</sup>.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The Chemistry Reviewer recommends approval of the NDA. Please see the review by Dr. Sheldon Markofsky dated October 28, 2013 for details. Also, a Biopharmaceutics Reviewer, Dr. Okpo Eradiri, reviewed dissolution methods and the acceptance criteria for canagliflozin and metformin HCl, active components in the FDC, and found them acceptable for approval. Please see his review dated July 26, 2013 for details.

The applicant referenced the canagliflozin NDA (204-402) for all CMC information on the drug substance canagliflozin hemihydrate, and referenced and provided a letter of authorization to DMF [REDACTED] <sup>(b) (4)</sup> (metformin HCl, USP) for all CMC information on the drug substance metformin hydrochloride.

The drug product is a fixed-dose combination consisting of canagliflozin anhydrous/metformin hydrochloride as immediate-release film-coated tablets with the strengths of 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg. The drug product also contains the following inactive ingredients in the core tablets: croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose. The film coating contains the following excipients: Macrogol/PEG, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow (50/1000 and 150/500 mg tablets only), iron oxide red

(50/1000, 150/500, 150/1000 mg tablets only), and iron oxide black (150/1000 mg tablet only).

The presence of a (b) (4) impurity (b) (4) also called (b) (4) in the drug substance and in the drug product was reported to the Agency in an amendment to NDA 204-042. (b) (4) was positive in the Ames test. Light and stress stability data showed that no significant increase in the levels of (b) (4) (b) (4) occurs in the drug substance over time. Dr. Markofsky concluded that the specifications are adequate, as the applicant agreed to the (b) (4) ppm limit in all strengths of the drug product (amendment submitted on June 28, 2013).

The product will be packaged in high density polyethylene bottles (HDPE) with desiccants.

A 24-month expiry is granted since the stability studies support an expiration dating period of 24 months for all strengths of Invokamet when stored at controlled room temperature (25°C or 77°F), with excursions permitted 15-30°C (59-86°F).

## 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology Reviewer recommends approval of the NDA. Please see the review by Dr. Fred Alavi dated August 21, 2013 for details. I have briefly summarized the main findings from his review below.

Most of the nonclinical pharmacology and toxicology data for the FDC are derived from data established for canagliflozin and metformin IR as individual components. The sponsor conducted a bridging 3-month toxicology study and an embryofetal development study in rats assessing canagliflozin in combination with metformin.

Similar to canagliflozin alone, a 3-month toxicology study with combination therapy showed a dose dependent increase in urinary glucose and calcium excretion which led to renal tubule and pelvic dilatation, and trabecular bone hyperostosis in rats. The addition of metformin did not have any additional impact on the toxicity profile of canagliflozin in rats. Although metformin had no effect on canagliflozin exposure, canagliflozin slightly increased metformin exposure (~1.4-1.8x), which was likely related to the canagliflozin-induced changes in renal hemodynamics affecting metformin's excretion in the kidneys.

In the embryofetal development study, administration of canagliflozin with or without metformin showed decreased maternal body weight and fetal skeletal variations. The

skeletal variations were likely to be related to maternal weight loss and likely represent delayed development. Dr. Alavi concluded that since these changes are transient, they are unlikely to be clinically meaningful.

Dr. Alavi concluded that the nonclinical studies support the approval of canagliflozin/metformin FDC for use in humans.

#### **4.4 Clinical Pharmacology**

At the time of writing this review, the Clinical Pharmacology Review has not been finalized. At the Late-Cycle Meeting with the applicant, the Clinical Pharmacologist conveyed the absence of a robust relationship between plasma canagliflozin concentrations and HbA1c response for canagliflozin. Therefore, the current PK/PD model as submitted in this NDA is inadequate to bridge the QD (as dosed in the canagliflozin program) and BID (as proposed in this FDC) dosing regimen. See the Late-Cycle Meeting Minutes for full details. In response to this review issue, the applicant submitted a new PK/PD analysis plan on October 15, 2013, but the Clinical Pharmacologists do not believe that their proposed plan would be adequate to bridge the efficacy of QD and BID dosing regimen due to limitations of the available data.

A brief summary is provided in this section based on the applicant's submission.

##### **4.4.1 Mechanism of Action**

Canagliflozin/metformin contains two antihyperglycemic agents with each agent having a distinct mechanism of action that may lead to improved glucose homeostasis compared to monotherapy. Canagliflozin is an orally active inhibitor of SGLT2 in the proximal tubule, and lowers plasma glucose levels by lowering the renal threshold for glucose and increasing urinary glucose excretion. The glycemic effect of canagliflozin is therefore not dependent on endogenous insulin secretion nor does it improve insulin sensitivity. Metformin lowers blood glucose by decreasing hepatic glucose production and improving insulin sensitivity through peripheral glucose reuptake and utilization. Metformin does not directly affect insulin secretion or metabolism.

##### **4.4.2 Pharmacodynamics**

The canagliflozin tablet is dosed once daily at 100 mg and 300 mg, whereas the canagliflozin/metformin IR FDC is to be dosed BID due to its metformin component. In the FDC, the canagliflozin component will be administered as 50 mg and 150 mg BID to provide the same total daily doses as canagliflozin single-agent.

In Phase 1 studies, canagliflozin 300 mg QD maximally reduced 24-hour renal threshold for glucose ( $RT_G$ ) and canagliflozin 150 mg QD provided near-maximal 24-hour reduction in  $RT_G$ .

In Phase 1 studies, 300 mg dose of canagliflozin provided greater reductions in postprandial glucose excursions than lower doses, without notable difference in urinary glucose excretion rate.

Canagliflozin 300 mg given before a meal reduced the postprandial glucose excursion, which was not seen with the 150 mg dose. This may be due to SGLT1 inhibition in the intestinal lumen with the higher dose, before the drug gets absorbed.

#### 4.4.3 Pharmacokinetics

Canagliflozin: The oral bioavailability of canagliflozin is about 65% and is rapidly absorbed with a  $t_{max}$  of 1-2 hours post-dose. Canagliflozin is extensively bound to plasma proteins (98 to 99%), mainly to albumin (97%), and as a result is negligibly removed by dialysis. In healthy individuals, 33% of canagliflozin after ingestion gets excreted in urine as glucuronide metabolites and 60% is excreted in feces. The mean terminal plasma half-life ( $t_{1/2}$ ) of canagliflozin was 10.6 and 13.1 hours with 100 mg and 300 mg dose respectively.

Metformin: The absolute bioavailability of metformin is about 50-60%. It is minimally bound to plasma proteins. Metformin is excreted unchanged in the urine, with tubular secretion as the major route of elimination. The half-life after an oral administration is about 6 hours in the plasma.

Canagliflozin and Metformin: In summary, key pharmacology trials demonstrated the following:

- Four pivotal bioequivalence (BE) trials (DIA1038, DIA1046, DIA1050, DIA1051) demonstrated the BE of canagliflozin/metformin IR FDC tablets to equal doses of the individual components;
- The food effect study (DIA1037) showed that the administration of 150/1000 mg canagliflozin/metformin IR FDC with a meal did not have any effects on the bioavailability of canagliflozin and the  $AUC_{\infty}$  of metformin, and decreased the  $C_{max}$  of metformin by 16%. The small decrease in metformin  $C_{max}$  was not considered to be clinically meaningful;
- A relative bioavailability study showed that the bioavailability of canagliflozin and metformin was similar after administration of the FDC tablets and co-administration of individual components (DIA1036). This served as a pilot for the four BE trials;
- The applicant also assessed the steady-state PK and PD after QD and BID dosing of canagliflozin in healthy subjects in an open-label, multiple dose study (DIA1032), which was reviewed by Dr. Jaya Vaidyanathan in the canagliflozin NDA; see her review dated February 6, 2013.

Also, in canagliflozin NDA, two canagliflozin-metformin drug-drug interaction studies (NAP1004 and DIA1028) have demonstrated a lack of clinically relevant drug-drug interactions between canagliflozin and metformin.

## 5 Sources of Clinical Data

The NDA 204353 was submitted in electronic Common Technical Document format, with the following link: <\\CDSESUB1\EVSPROD\NDA204353\204353.enx>

For the FDC, the applicant is referencing information from the canagliflozin single-agent NDA (204-042) and Glucophage NDA (020-357).

The evidence for efficacy and safety of the canagliflozin/metformin IR FDC is primarily from six Phase 3 trials that evaluated once daily administration of canagliflozin 100 mg or 300 mg in T2DM subjects as add-on to metformin (alone or in combination with another anti-hyperglycemic agent [AHA]). Canagliflozin was added to metformin alone in two trials (DIA3006 and DIA3009), to metformin in combination with another AHA in three trials (DIA3002, DIA3012, and DIA3015), and the Insulin Substudy of DIA3008 (Population 3) evaluated canagliflozin as add-on to insulin and metformin. A dose-ranging Phase 2 trial, DIA2001, also evaluated canagliflozin as add-on to metformin.

In order to bridge the results from the canagliflozin NDA (canagliflozin 100 mg and 300 mg once daily) to the FDC tablet (to be given BID at the total daily doses of 100 mg and 300 mg of canagliflozin), the following are newly conducted clinical data to support this FDC application:

- Four Phase 1 trials showing the bioequivalence of to-be-marketed canagliflozin/metformin IR FDC tablet to equal doses of the individual components (DIA1046, DIA1050, DIA1051, and DIA1038);
- A relative bioavailability study showing that the bioavailability of canagliflozin and metformin was similar after administration of the FDC tablets and co-administration of individual components (DIA1036);
- A food effect study with the to-be-marketed FDC tablet (DIA1037);
- A Phase 2, 18-week trial in T2DM comparing the efficacy, safety and tolerability of canagliflozin given BID (at total daily doses of 100 mg or 300 mg) to placebo as add-on to metformin.

In addition, the applicant had conducted a Phase 1 trial evaluating the PK and PD of canagliflozin QD dosing versus BID dosing in DIA1032, which was previously submitted in the canagliflozin NDA.

At the 4-Month Safety Update (4MSU), two additional trials with controlled extensions (DIA3004 and DIA3012) were completed. The 4MSU had a data cutoff date of

December 31, 2012, and provided an updated DS3 dataset from the canagliflozin NDA (which contains safety data from eight Phase 3 trials). The 4MSU updated key adverse event results, including the overall summary of adverse events, incidence of deaths, serious adverse events, discontinuations due to adverse events, and adverse events of fractures and malignancies.

## 5.1 Tables of Studies/Clinical Trials

Table 1 summarizes Phase 1 trials that the applicant conducted in support of the canagliflozin/metformin IR FDC.

**Table 1: Phase 1 Trials supporting the Canagliflozin/Metformin IR FDC**

<b>Trial</b>	<b>Trial Design</b>	<b>Primary Objective</b>	<b>N</b>
<b>DIA1032</b>	Randomized, open-label, single-center, multiple-dose, 2-period, 2 cohort, cross-ver study in healthy adult subjects	To evaluate the steady-state PK and PD of canagliflozin administered QD and BID	34
<b>DIA1036</b>	Randomized, open-label, single-center, single-dose, 2-period, 6 cohort, cross-over study in healthy fed adult subjects	To evaluate the PK and relative bioavailability of Cana and Met administered as 6 different FDC tablets relative to the individual components	85
<b>DIA1037*</b>	Randomized, open-label, single-center, single-dose, 2-period, 2-sequence, cross-over study in healthy adult subjects	To evaluate the effect of co-administration of a high fat meal on the oral bioavailability of a FDC tablet of Cana and Met IR	24
<b>DIA1038*</b>	Randomized, open-label, single-center, single-dose, 2-period, 2-sequence, cross-over study in healthy fed adult subjects	To evaluate the BE of Cana/Met IR FDC tablets 2x (150 mg/1000 mg) compared with equal doses of the individual components of canagliflozin (300 mg) and metformin IR (2x 1000 mg)	83
<b>DIA1046*</b>	Randomized, open-label, single-center, single-dose, 2-period, 2-sequence, cross-over study in healthy fed adult subjects	To evaluate the BE of Cana/Met IR FDC tablets 2x (50 mg/500) compared with equal doses of individual components of canagliflozin (100 mg) and metformin IR (2x 500 mg)	64
<b>DIA1050*</b>	Randomized, open-label, single-center, single-dose, 2-period, 2-sequence, cross-over study in healthy fed adult subjects	To evaluate the BE of Cana/Met IR FDC tablets 2x (150 mg/500) compared with equal doses of individual components of canagliflozin (300 mg) and metformin IR (2x 500 mg)	64
<b>DIA1051*</b>	Randomized, open-label, single-center, single-dose, 2-period, 2-sequence, cross-over study in healthy fed adult subjects	To evaluate the BE of Cana/Met IR FDC tablets 2x (50 mg/1000) compared with equal doses of individual components of canagliflozin (100 mg) and metformin IR (2x 1000 mg)	64

\*To-be-marketed formulation  
Source: ISS-addendum, Table 2

Table 2 summarizes all Phase 2 and 3 Trials supporting the canagliflozin/metformin IR FDC. Only DIA2003 was a new trial under the FDC NDA.

Clinical Review  
Hyon J. Kwon, PharmD, MPH  
NDA 204353  
Canagliflozin/metformin HCl IR FDC

**Table 2: Phase 2 and 3 Trials supporting the Canagliflozin/Metformin IR FDC**

Trial	Trial Design	Trial Population	Treatment Arms: # of Subjects Randomized	Duration
<b>Phase 2 Trials</b>				
<b>DIA2001</b> Add-on to Metformin	Randomized, double-blind, placebo and active-controlled, double-dummy, parallel group, dose-ranging trial	HbA1c 7 to 10.5% inclusive	Cana 50 mg QD: 64 Cana 100 mg QD: 64 Cana 200 mg QD: 65 Cana 300 mg QD: 64 Cana 300 mg BID: 64 Sitagliptin 100 mg QD: 65 Placebo QD: 65	12 weeks
<b>DIA2003</b> Add-on to Metformin IR	Randomized, double-blind, placebo-controlled, parallel group, 18-week trial	HbA1c 7 to 10.5% inclusive	Cana 50 mg BID: 93 Cana 150 mg BID: 93 Placebo BID: 93	18 weeks
<b>Phase 3 Trials</b>				
<b>DIA3006<sup>a</sup></b> Add-on to Metformin	Randomized, double-blind, placebo- and active-controlled, parallel group	T2DM subjects on metformin; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 368 Cana 300 mg: 367 Sitagliptin 100 mg: 366 Placebo: 183	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
<b>DIA3009</b> Add-on to Metformin	Randomized, double-blind, active-controlled, parallel group	T2DM subjects on metformin; HbA1c 7 to 9.5% inclusive	Cana 100 mg: 483 Cana 300 mg: 485 Glimepiride: 482	104 weeks (52-week active-controlled, core double-blind period plus a 52-week active-controlled, extension double-blind period )
<b>DIA3002</b> Add-on to Metformin + SU	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 157 Cana 300 mg: 156 Placebo: 156	52 weeks (26-week placebo-controlled, core double-blind period plus a 26-week placebo-controlled, extension double-blind period )
<b>DIA3012<sup>a</sup></b> Add-on to Metformin + Pioglitazone	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects on metformin + pioglitazone therapy; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 113 Cana 300 mg: 114 Placebo: 115	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
<b>DIA3015</b> Add-on to Metformin + SU	Randomized, double-blind, active-controlled, parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10.5% inclusive	Cana 300 mg: 377 Sitagliptin 100 mg: 378	52 weeks
<b>DIA3008</b> Insulin Substudy (Population 3) Add-on to insulin + metformin	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects on insulin $\geq$ 30 units/day + metformin $\geq$ 2000 mg/day; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 139 Cana 300 mg: 148 Placebo: 145	18 weeks

<sup>a</sup>Subjects assigned to placebo were switched to sitagliptin during the double-blind extension period

Abbreviations: Cana=canagliflozin; SU=sulfonylurea; AHA=antihyperglycemic agent; CV=cardiovascular; QD=daily; BID=twice daily

Source: Modified from Module 2.5 Clinical Overview, Tables 2 and 3

## 5.2 Review Strategy

The canagliflozin/metformin IR FDC NDA relies on data from Phase 3 trials that provided the primary support for the canagliflozin NDA, with additional clinical data from a new Phase 2 trial, DIA2003, an 18-week Phase 2 trial evaluating canagliflozin BID as add-on to metformin. Also, Phase 1 pharmacology trials evaluated the PK bioequivalence of the to-be-marketed canagliflozin/metformin IR FDC to the equal doses of individual components.

I did not re-review the Phase 3 trials that were previously reviewed under the canagliflozin NDA 204-042. My efforts were concentrated on reviewing the new data or analysis from trials presented under the current NDA in support of FDC, mainly:

1. The results of four pivotal pharmacology trials showing bioequivalence between the to-be-marketed FDC and coadministration of canagliflozin and metformin at equal doses;
2. The efficacy and safety results of a new Phase 2 trial (DIA2003) conducted in support of canagliflozin BID dosing;
3. The safety data from a pooled dataset combining three 26-week placebo-controlled Phase 3 trials (DIA3002, DIA3006, and DIA3012) that evaluated the efficacy and safety of canagliflozin as add-on to metformin, either alone or in combination with other AHAs, in order to evaluate whether the safety of canagliflozin added to ongoing metformin therapy showed any differences from the established safety profile of canagliflozin NDA;
4. The updated safety information contained in the 4-Month Safety Update, submitted by the applicant on April 9, 2013.

It should be noted that the results of DIA3008 Insulin Substudy were reviewed in the canagliflozin NDA, but the efficacy results discussed from this substudy were from Population 2 (subjects who were taking insulin  $\geq 30$  IU/day). Therefore, the efficacy results from Population 3 (subjects who were taking insulin  $\geq 30$  IU/day and metformin  $> 2000$  mg/day) of DIA3008 Insulin Substudy in support of this FDC are presented in section 6.

## 5.3 Discussion of Individual Studies/Clinical Trials

As all the Phase 3 trials were previously reviewed in the canagliflozin NDA, see my review of NDA 204-042 for discussion of Phase 3 trials. The placebo-controlled Phase 3 trials primarily supporting the canagliflozin/metformin FDC, DIA3006, DIA3002, and DIA3012, had a core double-blind period with the primary endpoint at 26 weeks, and the DIA3008 Insulin Substudy/Population 3 had a core double-blind period of 18 weeks. In

the 2 active-comparator, noninferiority trials (DIA3009 [versus glimepiride, background of metformin] and DIA3015 [versus sitagliptin, background of metformin and SU]), the primary endpoint was evaluated at 52 weeks.

In addition, DIA2001 was also discussed in the canagliflozin NDA.

Only DIA2003 is summarized here, as this is a newly conducted Phase 2 trial in support of this FDC application.

### **DIA2003:**

#### Objectives:

- Primary – After 18 weeks, 1) To assess the effect of canagliflozin 150 mg administered twice daily compared to placebo on HbA1c; 2) To assess the safety and tolerability of canagliflozin;
- Secondary – After 18 weeks, 1) To assess the effect of canagliflozin 50 mg administered twice daily compared to placebo on HbA1c; 2) To assess the effect of canagliflozin 150 mg or 50 mg twice daily compared to placebo on FPG, body weight, proportion of subjects with HbA1c <7 and <6.5%, fasting plasma lipids (LDL-C, HDL-C, total cholesterol, LDL-C to HDL-C ratio, and triglycerides); systolic and diastolic blood pressure.

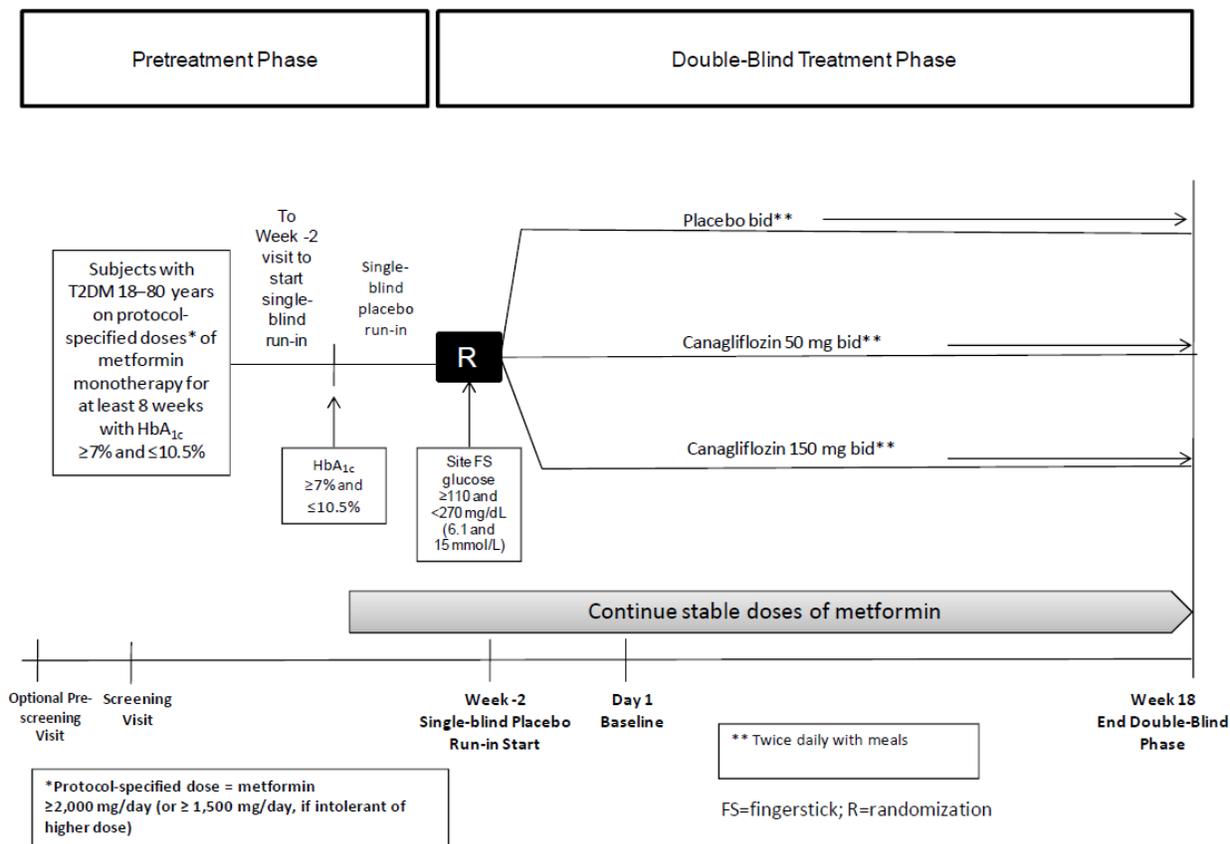
Study Design: DIA2003 was an 18-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 2 trial evaluating the efficacy and safety of canagliflozin BID dosing in T2DM subjects with inadequate glycemic control on maximal or near maximal effective dose of metformin monotherapy ( $\geq 2000$  mg/day, or  $\geq 1500$  mg/day if unable to tolerate for at least 8 weeks).

The primary objective and key secondary objective of this trial was to demonstrate the superiority of canagliflozin 150 mg and 50 mg BID compared to placebo, as measured by the change in HbA1c from baseline to Week 18.

Eligible subjects were randomized in a 1:1:1 ratio to the addition of canagliflozin 50 mg BID, canagliflozin 150 mg BID, or matching placebo BID, to the ongoing stable dose of metformin monotherapy. Randomization was stratified by baseline HbA1c value (< or  $\geq 8\%$ ).

After screening, eligible subjects entered a 2-week single-blind placebo run-in period before entering an 18-week, placebo-controlled, double-blind treatment period. Figure 1 shows an overview of DIA2003 study design.

Figure 1: Overview of DIA2003 Study Design



Source: CSR DIA2003, Figure 1

Subjects were to maintain their background metformin therapy throughout the run-in and double-blind treatment period unless dose adjustment was necessary due to intolerance. No other AHAs were allowed during the study. Concurrent antihypertensive and lipid-lowering drugs were allowed and subjects were required to be on a stable regimen for at least 4 weeks before randomization.

Safety evaluations included adverse events, laboratory tests, 12-lead ECGs, vital signs, body weight, physical examinations, self-monitored blood glucose, and hypoglycemic episodes.

Unlike Phase 3 trials with canagliflozin, rescue therapy was not permitted in this trial. Subjects were withdrawn from the trial if they exceeded the following FPG values, repeated and confirmed within 7 days: fasting plasma glucose (FPG) >270 mg/dL from baseline through Week 6, FPG >240 mg/dL from Week 6 through Week 12, and FPG >200 mg/dL from Week 12 through Week 18.

Subjects were also discontinued if: eGFR was  $<50$  mL/min/1.73 m<sup>2</sup>, or serum creatinine  $\geq 1.5$  mg/dL for men and  $\geq 1.4$  mg/dL for women.

Similar to other Phase 3 trials with canagliflozin, an independent CV event adjudication committee reviewed and adjudicated the following events: all major adverse cardiovascular events (MACE) including CV death, nonfatal MI, and nonfatal stroke, plus events of hospitalized unstable angina. Other adverse events that were adjudicated included hospitalization for congestive heart failure, deep vein thrombosis/pulmonary embolism, fractures, and skin adverse events. An independent assessment committee did an additional assessment of hepatic and renal events.

Inclusion Criteria:

- Male or female 18 to 80 years of age with T2DM and on metformin monotherapy at a stable protocol-specified dose ( $\geq 2000$  mg/day, or  $\geq 1500$  mg/day if unable to tolerate a higher dose) for at least 8 weeks before screening, with HbA1c of 7 to 10.5% at screening, inclusive;
- FPG  $<270$  mg/dL at the start of run-in period;
- Fasting fingerstick glucose of  $\geq 110$  mg/dL and  $<270$  mg/dL at home or at the investigational site on baseline.

Exclusion Criteria:

- History of diabetic ketoacidosis, type 1 diabetes mellitus, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy;
- Repeat (2 or more over a one-week period) FPG and/or fasting SMBG  $\geq 270$  mg/dL before the start of run-in period, despite diet and exercise counseling;
- On either PPAR-gamma agonist, ongoing insulin therapy, another SGLT2 inhibitor, or any AHA other than metformin within 12 weeks before screening;
- Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months of screening; or planned revascularization, or have a history of NYHA Class 3-4 heart disease;
- Findings on 12-lead ECG that required urgent diagnostic evaluation or intervention;
- Uncontrolled hypertension (i.e., average of 3 seated blood pressure with DBP  $\geq 100$  mmHg or SBP  $\geq 160$  mmHg) at the start of run-in period;
- Estimated glomerular filtration rate (eGFR)  $<55$  mL/min/1.73m<sup>2</sup> (or eGFR  $<60$  mL/min/1.73m<sup>2</sup> based on the metformin local label), or serum creatinine  $\geq 1.4$  mg/dL for men and  $\geq 1.3$  mg/dL for women.

Statistical Methods: The primary efficacy endpoint was the change in HbA1c from baseline to Week 18. The statistical methods for DIA2003 were consistent with other Phase 3 trials with canagliflozin.

The primary efficacy endpoint comparing each canagliflozin group to placebo was analyzed with an analysis of covariance (ANCOVA) model with treatment and stratification factor as fixed effects and the baseline HbA1c as a covariate. The least-squared (LS) means for the treatment differences between each canagliflozin group and placebo and their two-sided 95% confidence interval were estimated using this model. Supportive analyses were conducted based on the per-protocol (PP) analysis set, using mixed model repeated measures (MMRM), and 18-week completers' analysis set.

The secondary efficacy endpoints included change from baseline to Week 18 in FPG, % change from baseline to Week 18 in body weight, and proportion of subjects with HbA1c <7% at Week 18. Changes in FPG and body weight were analyzed using an ANCOVA model similar to the primary efficacy endpoint. The proportion of subjects with HbA1c <7% at Week 18 was analyzed using a logistic regression model including terms for treatment and stratification factor, and adjusted for the baseline HbA1c as a covariate.

Type 1 error was controlled at 5% by sequential testing of hypotheses, as following:

1. Cana 150 mg BID superiority vs. placebo in HbA1c reduction;
2. Cana 50 mg BID superiority vs. placebo in HbA1c reduction;
3. Cana 150 mg BID superiority vs. placebo in FPG reduction;
4. Cana 50 mg BID superiority vs. placebo in FPG reduction;
5. Cana 150 mg BID superiority vs. placebo in body weight reduction;
6. Cana 50 mg BID superiority vs. placebo in body weight reduction;
7. Cana 150 mg BID superiority vs. placebo achieving HbA1c target of <7%;
8. Cana 50 mg BID superiority vs. placebo achieving HbA1c target of <7%.

The primary and secondary efficacy analyses were based on the modified intent-to-treat (mITT) analysis set, which included all randomized subjects who received at least one dose of study drug. Supportive analyses were done based on the per protocol (PP) analysis set, which included all mITT subjects who completed 18-week and had no major protocol deviations that may affect the interpretation of the primary efficacy endpoint.

Missing data for efficacy variable was imputed using the last-observation-carried-forward (LOCF) method in the mITT efficacy analyses. For analyses of the change from baseline for efficacy endpoints, only subjects with both baseline and at least one post-baseline measure were included.

The safety analyses were done using the 'as treated' population.

## 6 Review of Efficacy

### **Efficacy Summary**

The efficacy supporting the combined use of canagliflozin and metformin in the target indication was evaluated in six Phase 3 trials where canagliflozin was added to the background metformin therapy. These six Phase 3 trials included subjects on metformin alone (DIA3006 and DIA3009), and metformin in combination with another AHA (DIA3002, DIA3015, DIA3012, and DIA3008 Insulin Substudy/Population 3). For all these trials that required metformin as background therapy, metformin dose  $\geq 2000$  mg/day (or  $\geq 1500$  mg/day for those intolerant) was required.

These Phase 3 trials have demonstrated that once-daily administration of canagliflozin 100 mg and 300 mg as add-on to metformin provided a clinically meaningful and statistically significant reduction in HbA1c. The placebo-adjusted HbA1c reduction with canagliflozin as add-on to metformin in four placebo-controlled Phase 3 trials (DIA3002, DIA3006, DIA3012, DIA3008 Insulin Substudy/Population 3) was statistically significant and ranged from -0.62 to -0.71% with 100 mg QD and -0.76 to -0.92% with 300 mg QD after 24 weeks (DIA3002, DIA3006, DIA3012) or 18 weeks (DIA3008 Insulin Substudy/Population 3).

In two active-controlled trials, the non-inferiority of canagliflozin 100 mg and 300 mg QD as add-on to metformin was demonstrated when compared to glimepiride (DIA3009), and non-inferiority of canagliflozin 300 mg QD was demonstrated when compared to sitagliptin (DIA3015).

In all Phase 3 trials, canagliflozin 100 mg and 300 mg was administered once daily. Because the canagliflozin/metformin IR FDC contains metformin IR, the FDC tablet is to be dosed twice daily with meals. Thus, as a component of the FDC product, canagliflozin is to be administered 50 mg or 150 mg twice daily to provide the same total daily doses studied in Phase 3 trials. In order to provide clinical data for twice daily dosing with canagliflozin, the applicant conducted an 18-week Phase 2 trial (DIA2003) specifically for this FDC. DIA2003 evaluated the efficacy and safety of canagliflozin administered as 50 mg and 150 mg BID as add-on to metformin.

In DIA2003, the placebo-adjusted LS mean changes in HbA1c from baseline to Week 18 were -0.44% and -0.60% for canagliflozin 50 mg BID and 150 mg BID respectively ( $p < 0.001$  for both comparisons). This magnitude of HbA1c lowering observed with BID dosing in DIA2003 was numerically smaller compared to the reduction observed in Phase 3 trials where canagliflozin was administered once daily. For example, DIA3006 is a Phase 3 trial with similar study design as DIA2003 including subject enrollment criteria but with a longer treatment period (26 weeks instead of 18 weeks), and the placebo-adjusted LS mean changes in HbA1c from baseline to Week 26 were -0.62%

and -0.77% for canagliflozin 100 mg QD and 300 mg QD respectively ( $p < 0.001$  for both comparisons). The HbA1c reductions at Week 18 in DIA3006 were numerically similar to Week 26 results.

In addition, the placebo-adjusted LS mean changes in FPG with both canagliflozin groups in DIA2003 were similar (-23.6 mg/dL and -24.0 mg/dL with canagliflozin 50 mg and 150 mg BID respectively) and did not demonstrate any incremental benefit with the higher dose of canagliflozin, and was numerically smaller compared to similarly designed Phase 3 trial DIA3006 (-30 mg/dL and -40 mg/dL with canagliflozin 100 mg and 300 mg QD respectively).

Therefore, the clinical data submitted in the FDC NDA have not adequately demonstrated that BID administration of canagliflozin would provide similar glycemic control as QD administration of canagliflozin at the same total daily doses.

## 6.1 Indication

The proposed indication for the canagliflozin/metformin IR FDC is use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

(b) (4)

### 6.1.1 Methods

The Phase 2 and Phase 3 clinical trials that provided the primary support for the canagliflozin NDA (204-042) also provided the primary support for the FDC of canagliflozin with metformin. One Phase 2 trial (DIA2001) and six Phase 3 trials (DIA3002, DIA3006, DIA3012, DIA3009, DIA3015, DIA3008 Insulin Substudy/Population 3) evaluated the efficacy of canagliflozin as add-on to metformin, alone or in combination with other AHA. In all the Phase 2 and 3 trials, canagliflozin and metformin were given as individual tablets and not as FDC.

Also, in all the Phase 3 trials, 100 mg and 300 mg of canagliflozin was administered once daily. As discussed, the FDC contains metformin IR and the FDC tablet is to be dosed twice daily with meals, with the canagliflozin component to be administered as 50 mg and 150 mg BID to provide the same total daily doses studied in Phase 3 trials. Thus, in order to provide clinical data for twice daily dosing with canagliflozin, a Phase 2 trial (DIA2003) was conducted specifically for this FDC in order to evaluate the safety and efficacy of canagliflozin BID regimen as add-on to metformin therapy.

Since the efficacy of Phase 3 trials has already been discussed in my review of the canagliflozin NDA, the efficacy section in this document will mainly focus on the results of DIA2003 and any relevant discussion related to its results.

## 6.1.2 Demographics

### DIA2003

The demographic and diabetic baseline characteristics in DIA2003 for each treatment group are summarized in Table 3. The median age of all subjects was 57 years (range 26 to 80 years), and most (83%) subjects were Caucasian. The mean baseline HbA1c was 7.6%, and about 22% of subjects had baseline HbA1c <7%. The mean duration of diabetes was 7 years, with a median of 5.5 years.

**Reviewer’s comment: Overall, the baseline characteristics of subjects participating in DIA2003 were similar to six Phase 3 trials that evaluated canagliflozin as add-on to metformin, except for baseline HbA1c. The mean baseline HbA1c was slightly lower in DIA2003 (7.6%) compared to the Phase 3 trials (range 7.8 to 8.4%).**

**Table 3: Baseline Characteristics - DIA2003**

Baseline Characteristic	Placebo (N=93)	Cana 50 mg BID (N=93)	Cana 150 mg BID (N=93)
Age (mean years [SD])	57 (9)	59 (9)	58 (10)
Gender (male, n [%])	46 (50%)	40 (43%)	44 (47%)
BMI, kg/m <sup>2</sup> (mean [SD])	32.3 (5.7)	33 (7.0)	32.3 (6.8)
HbA1c, % (mean [SD])	7.7 (0.9)	7.6 (0.9)	7.6 (0.9)
Duration of diabetes (years mean [SD])	7.0 (6.4)	6.7 (4.9)	7.3 (6.0)
Baseline eGFR, mL/min/1.73 <sup>2</sup> (mean [SD])	84.8 (16.5)	86.9 (18.0)	85.9 (15.3)
Race			
White (n [%])	73 (79%)	75 (81%)	83 (89%)
Black or African Americans	4 (4%)	5 (5%)	1 (1%)
Asian	9 (10%)	3 (3%)	6 (7%)
American Indian or Alaska Native	0	1 (1%)	0
Native Hawaiian	0	0	1 (1.1%)
Multiple	1 (1%)	0	0
Other	6 (7%)	9 (10%)	2 (2%)

Source: CTR DIA2003, Table 5, 6, and 7

## 6.1.3 Subject Disposition

### DIA2003

A total of 279 subjects were randomized (93 subjects in each treatment group), and 90% of randomized subjects completed 18 weeks of treatment. Twenty-eight subjects discontinued the study drug before 18 weeks, and a higher proportion of subjects in the canagliflozin 150 mg BID group discontinued the trial before 18 weeks compared to canagliflozin 50 mg BID or placebo groups (14% compared to 8.6% and 7.5% respectively, see Table 4).

Among subjects who completed the 18-week study period, two subjects (one in each canagliflozin groups) had major protocol violations and were excluded from the Per-Protocol analysis set. One subject changed the background metformin dose and the other subject received the wrong double-blind study drug.

**Table 4: Subject Disposition in DIA2003**

	Placebo (N=93) n (%)	CANA 50 mg bid (N=93) n (%)	CANA 150 mg bid (N=93) n (%)	CANA Total (N=186) n (%)	Total (N=279) n (%)
Subjects who are randomized	93 (100)	93 (100)	93 (100)	186 (100)	279 (100)
Subjects in the mITT analysis set	93 (100)	93 (100)	93 (100)	186 (100)	279 (100)
Subjects in the safety analysis set	93 (100)	93 (100)	93 (100)	186 (100)	279 (100)
mITT subjects who discontinued before the Week 18 visit	7 (7.5)	8 (8.6)	13 (14.0)	21 (11.3)	28 (10.0)
Subjects in the Completers' analysis set	86 (92.5)	85 (91.4)	80 (86.0)	165 (88.7)	251 (90.0)
mITT subjects in the PP analysis set	86 (92.5)	84 (90.3)	79 (84.9)	163 (87.6)	249 (89.2)

NOTE: Percentage calculated with the number of subjects in each group as denominator  
Source: CTR DIA2003, Table 2

The most common reason for study discontinuation was due to an adverse event, as shown in Table 3. The largest cause for discontinuations seen with the 150 mg BID group was mainly due to adverse events; 7 subjects (7.5%) in the canagliflozin 150 mg BID group discontinued the trial due to adverse events compared to 1 subject (1.1%) in the canagliflozin 50 mg BID group and none in the placebo group. Adverse events leading to study discontinuation is further discussed in Dropouts and/or Discontinuations (section 7.3.3).

Very few subjects in each treatment arm discontinued due to "Other" reasons, which were due to relocation, extended travel, and poor compliance with study visits.

**Table 5: Reasons for Study Discontinuation in DIA2003**

Subject Disposition Category	Placebo	CANA	CANA	CANA Total	Total
	(N=93) n (%)	50 mg bid (N=93) n (%)	150 mg bid (N=93) n (%)	(N=186) n (%)	(N=279) n (%)
<b>Primary reason for discontinuation *</b>					
Adverse event	7 ( 7.5)	8 ( 8.6)	13 (14.0)	21 (11.3)	28 (10.0)
Creatinine or eGFR withdrawal criteria	0	1 ( 1.1)	7 ( 7.5)	8 ( 4.3)	8 ( 2.9)
Lost to follow-up	0	1 ( 1.1)	2 ( 2.2)	3 ( 1.6)	3 ( 1.1)
Withdrawal of consent	2 ( 2.2)	0	2 ( 2.2)	2 ( 1.1)	4 ( 1.4)
Subject meets glycemic withdrawal criteria	2 ( 2.2)	4 ( 4.3)	0	4 ( 2.2)	6 ( 2.2)
Other	2 ( 2.2)	0	0	0	2 ( 0.7)
	1 ( 1.1)	2 ( 2.2)	2 ( 2.2)	4 ( 2.2)	5 ( 1.8)

NOTE: Percentage calculated with the number of subjects in each group as denominator  
Source: CTR DIA2003, Table 3

### 6.1.4 Analysis of Primary Endpoint(s)

#### Phase 3 Trials

The efficacy results from six Phase 3 trials providing the primary support for the canagliflozin/metformin IR FDC are summarized in Table 6. The placebo-adjusted HbA1c reduction with canagliflozin as add-on to metformin in four placebo-controlled Phase 3 trials ranged from -0.62 to -0.71% with 100 mg QD and -0.76 to -0.92% with 300 mg QD.

**Table 6: Summary of Changes in HbA1c From Baseline to Endpoint in Phase 3 Trials Providing Primary Support for Canagliflozin/Metformin IR FDC - mITT (LOCF)**

Study (Weeks)	Treatment Arm	N	Baseline Mean ± SE	LS Mean Change ± SE	LS mean difference (95% CI)	p-value
<b>Dual Therapy</b>						
<b>DIA3006</b> (26) Add-on to metformin	Cana 300 mg	360	7.95 ± 0.05	-0.94 ± 0.04	-0.77(-0.91,-0.64)	<.0001
	Cana 100 mg	365	7.94 ± 0.05	-0.79 ± 0.04	-0.62 (-0.76,-0.48)	<.0001
	Placebo	181	7.96 ± 0.07	-0.17 ± 0.06		
<b>Triple Therapy</b>						
<b>DIA3002</b> (26) Add on to metformin+SU	Cana 300 mg	152	8.13 ± 0.08	-1.06 ± 0.08	-0.92 (-1.11, -0.73)	<.0001
	Cana 100 mg	155	8.13 ± 0.07	-0.85 ± 0.08	-0.71 (-0.90, -0.52)	<.0001
	Placebo	150	8.12 ± 0.07	-0.13 ± 0.08		
<b>DIA3012</b> (26) Add on to metformin+PIO	Cana 300 mg	112	7.84 ± 0.09	-1.03 ± 0.07	-0.76 (-0.95, -0.57)	<.0001
	Cana 100 mg	113	7.99 ± 0.09	-0.89 ± 0.07	-0.62 (-0.81, -0.44)	<.0001
	Placebo	114	8.00 ± 0.09	-0.26 ± 0.07		
<b>Add-on to Insulin</b>						
<b>DIA3008 Substudy</b> (18) - Population 3	Cana 300 mg	148	8.22 (0.80)*	-0.79± 0.05	-0.82 (-0.96, -0.67)	<0.001
	Cana 100 mg	139	8.20 (0.86)*	-0.64± 0.06	-0.66 (-0.82, -0.51)	<0.001
	Placebo	145	8.15 (0.81)*	0.03 ± 0.05		
<b>Active-Comparator</b>						
<b>DIA3009</b> (52) Add-on to metformin	Cana 300 mg	474	7.79 ± 0.04	-0.93 ± 0.04	-0.12 (-0.22, -0.02)	0.0158
	Cana 100 mg	478	7.78 ± 0.04	-0.82 ± 0.04	-0.01 (-0.11, 0.09)	0.8074
	Glimepiride	473	7.83 ± 0.04	-0.82 ± 0.04		
<b>DIA3015</b> (52) Add on to metformin+SU	Cana 300 mg	365	8.13 ± 0.05	-0.66 ± 0.05	-0.37 (-0.50, -0.25)	<.0001
	Sitagliptin	374	8.12 ± 0.05	-1.03 ± 0.05		

Source: NDA204402 Clinical Review, Table 13, except for DIA3008 Substudy, CSR DIA3008-ins, Table 35  
\*SD

### DIA2001

Clinically meaningful reductions in HbA1c were seen with canagliflozin 100 mg and 300 mg QD compared to placebo at Week 12, as shown in Table 6. The placebo-subtracted LS mean changes in HbA1c from baseline at Week 12 were -0.51% and -0.71% with canagliflozin 100 mg and 300 mg QD respectively.

**Table 7: Summary of Changes in HbA1c from Baseline to Week 12 in DIA2001**

Study (Weeks)	Treatment Arm	N	Baseline Mean (SD)	LS Mean Change	LS mean difference (95% CI)	p-value
<b>DIA2001</b> (12) Add-on to metformin	Cana 300 mg QD	60	7.70 (1.04)	-0.92	-0.71 (-1.01,-0.41)	<.0001
	Cana 100 mg QD	62	7.81 (0.97)	-0.76	-0.51 (-0.80,-0.21)	<.0001
	Placebo	61	7.71 (0.83)	-0.22		

### DIA2003

The primary efficacy endpoint in DIA2003 was the change in HbA1c from baseline at Week 18, using the LOCF approach. As shown in Table 4, the placebo-adjusted LS mean change in HbA1c from baseline to Week 18 was -0.44% and -0.60% for canagliflozin 50 mg BID and 150 mg BID respectively, and reached statistical significance ( $p < 0.001$  for both comparisons). The results of sensitivity analyses such as PP analysis, completers' analysis, and MMRM were consistent and supported the primary analysis.

**Table 8: Summary of Changes in HbA1c from Baseline to Week 18 in DIA2003**

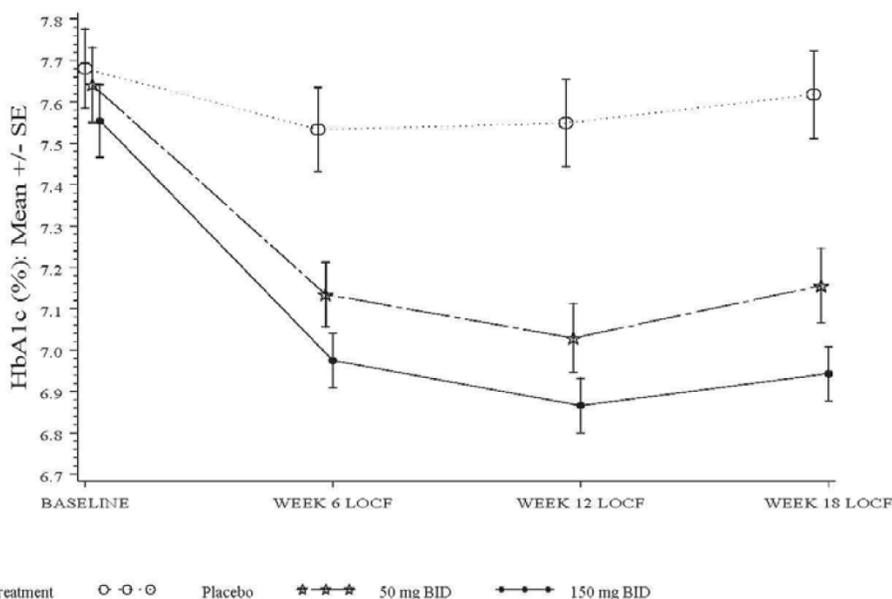
Study (Weeks)	Treatment Arm	N	Baseline Mean (SD)	LS Mean Change	LS mean difference (95% CI)	p-value
DIA2003 (18) Add-on to metformin	Cana 150 mg BID	91	7.53 (0.83)	-0.61	-0.60 (-0.79,-0.41)	<.0001
	Cana 50 mg BID	90	7.63 (0.84)	-0.45	-0.44 (-0.64,-0.25)	<.0001
	Placebo	92	7.66 (0.91)	-0.01		

Source: CSR DIA2003, Table 9

**Reviewer's comment: The glycemic efficacy observed in DIA2003 with canagliflozin BID dosing as add-on to metformin was less than observed in the placebo-controlled Phase 2 and 3 trials where canagliflozin was administered once daily as add-on to metformin. This is further discussed in section 6.1.10, Additional Efficacy Issues/Analyses.**

The LS mean change from baseline in HbA1c over time for each treatment group is shown in Figure 2. The HbA1c reduction appears to have reached a nadir by Week 12.

**Figure 2: Mean Change in HbA1c From Baseline Over Time in DIA2003 - LOCF**



Source: CSR DIA2003, Figure 4

### 6.1.5 Analysis of Secondary Endpoints(s)

#### DIA2003

Table 9 summarizes observed changes in the secondary endpoints from baseline to Week 18 in DIA2003, which are changes in FPG, body weight, and proportion of subjects achieving HbA1c <7.

**Table 9: DIA2003 Summary of Changes in Secondary Endpoints from Baseline to Week 18 - LOCF**

Treatment Arm	N	Baseline Mean (SD)	LS Mean Change ± SE	LS mean difference (95% CI)	p-value
<b>Fasting Plasma Glucose (mg/dL)</b>					
Cana 150 mg BID	91	163.1 (34.2)	-15.9 ±3.2	-24.0 (-33.2, -15.0)	<0.001
Cana 50 mg BID	90	161.1 (35.1)	-15.5 ±3.2	-23.6 (-32.4, -14.8)	<0.001
Placebo	92	161.6 (33.7)	8.1 ±3.2		
<b>Body Weight (kg)</b>					
Cana 150 mg BID	91	90.4 (18.9)	-3.2 ± 3.5	-2.6 (-3.5, -1.7)	<0.001
Cana 50 mg BID	90	90.6 (23.2)	-2.8 ± 0.3	-2.2 (-3.1, -1.3)	<0.001
Placebo	92	90.4 (18.2)	-0.6 ± 0.3		
<b>Proportion of subjects achieving HbA1c &lt;7%</b>					
Treatment Arm	N	% achieving target <7%	% Diff (minus placebo)	Odds Ratio vs placebo (95% CI)	p-value
Cana 150 mg BID	91	57.1%	25.6%	3.38 (1.68, 6.81)	<0.001
Cana 50 mg BID	90	47.8%	16.3%	2.43 (1.21, 4.90)	<0.013
Placebo	92	31.5%			

Source: CSR DIA2003, Table 11, 13, and 14.

The LS mean change from baseline to Week 18 in FPG was statistically significant for both canagliflozin groups compared to the placebo group (p<0.001): the placebo-adjusted LS mean changes in FPG were -23.6 mg/dL and -24.0 mg/dL with canagliflozin 50 mg and 150 mg BID respectively.

**Reviewer’s comment: The observed reductions in FPG with both canagliflozin groups were similar and did not demonstrate any incremental benefit with the higher dose of canagliflozin (i.e., canagliflozin 150 mg BID) in DIA2003. This is in contrast to the results of DIA3006, a similarly designed Phase 3 trial where canagliflozin was administered once daily at the same total dose as add-on to metformin. In DIA3006, the placebo-adjusted LS mean changes from baseline to Week 26 were -30 mg/dL and -40 mg/dL with canagliflozin 100 mg and 300 mg QD respectively (see my review of the canagliflozin NDA).**

The placebo-subtracted proportion of subjects who achieve HbA1c <7% was about 16% with canagliflozin 50 mg BID and 26% with canagliflozin 150 mg BID.

### 6.1.6 Other Endpoints

The changes from baseline to Week 18 in systolic and diastolic blood pressure in DIA2003 are summarized in Table 10.

**Table 10: DIA2003 - Change from Baseline to Week 18 in Blood Pressure**

Treatment Arm	N	Baseline Mean (SD)	Change from baseline $\pm$ SE	LS mean difference (95% CI)
<b>Systolic Blood Pressure</b>				
Cana 150 mg BID	91	128.2 (12.0)	-2.4 $\pm$ 1.1	-5.7 (-8.7, -2.6)
Cana 50 mg BID	90	131.1 (12.4)	-2.1 $\pm$ 1.1	-5.4 (-8.4, -2.3)
Placebo	92	128.6 (11.0)	3.3 $\pm$ 1.1	
<b>Diastolic Blood Pressure</b>				
Cana 150 mg BID	91	78.5 (7.7)	-1.8 $\pm$ 0.7	-3.1 (-5.0, -1.1)
Cana 50 mg BID	90	78.1 (7.4)	-1.2 $\pm$ 0.7	-2.4 (-4.3, -0.4)
Placebo	92	77.8 (7.2)	1.2 $\pm$ 0.7	

Source: CSR DIA2003, Table 16, 17

### 6.1.7 Subpopulations

See my review of canagliflozin NDA for discussion of subgroup analysis for a pooled dataset. The number of subjects in DIA2003 was too small to conduct a meaningful subgroup analysis.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The canagliflozin program supports 100 mg and 300 mg QD doses as add-on to metformin. The canagliflozin/metformin IR FDC is to be given twice daily with meals due to metformin IR posology, and as a result, the total daily dose of canagliflozin will be divided and administered twice daily in the FDC (i.e., 50 mg and 150 mg BID).

The applicant is bridging QD and BID dosing with the results from a Phase 2 trial (DIA2003) where the efficacy and safety of canagliflozin 50 mg and 150 mg BID were evaluated, and a Phase 1 trial (DIA1032) comparing the PK/PD of canagliflozin QD versus BID dosing.

**Reviewer's comment: As discussed in section 6.1.10, bridging of canagliflozin QD dosing from the Phase 3 program to BID dosing for FDC is not supported by the efficacy results from DIA2003. Also, as discussed during our Late-Cycle meeting with the applicant, the Clinical Pharmacologist concluded that the PK/PD model based on the data submitted in this NDA is inadequate to bridge the QD and BID dosing regimen for canagliflozin.**

Since metformin IR is recommended to be given with a meal to reduce the occurrence of gastrointestinal side effects, the applicant is recommending that the canagliflozin/metformin IR FDC be taken with a meal. In the Phase 3 program, canagliflozin was administered once daily before breakfast (i.e., under fasting conditions). To support administration of the canagliflozin/metformin IR FDC with meals, the applicant conducted a food effect study. DIA1037 demonstrated that the administration of to-be-marketed 150/1000 mg canagliflozin/metformin IR FDC with a meal had no effects on the bioavailability of canagliflozin and the  $AUC_{\infty}$  of metformin, and decreased the  $C_{max}$  of metformin by 16%. This small decrease in metformin  $C_{max}$  is not considered to be clinically meaningful.

As discussed in the canagliflozin NDA, a Phase 1 trial (DIA1045) has shown that canagliflozin 300 mg taken before a meal may provide some additional glycemic efficacy by lowering post-prandial glucose excursions, but this effect was not seen at the 150 mg dose. This effect has been postulated to be related to the inhibition of SGLT1 in the gut lumen. By splitting the total daily dose of canagliflozin for BID dosing, administration of canagliflozin 150 mg dose BID with FDC may not provide the additional glycemic lowering effect possible with a 300 mg QD dose of canagliflozin.

#### **6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

See my review of the canagliflozin NDA for discussion of persistence of efficacy.

#### **6.1.10 Additional Efficacy Issues/Analyses**

DIA2003 was a Phase 2 trial conducted to support the BID dosing for the FDC, as canagliflozin was administered once daily in Phase 3 trials. But DIA2003 compared the glycemic efficacy of canagliflozin BID dosing groups to placebo and did not have a comparative canagliflozin QD dosing group within the trial to evaluate whether QD and BID dosing at the same total daily dose would result in similar glycemic control.

In order to evaluate the glycemic efficacy of canagliflozin QD and BID at the same total daily doses, the HbA1c reduction observed in DIA2003 was compared to DIA3006, a similarly designed Phase 3 trial evaluating canagliflozin QD as add-on to metformin. As shown in Table 11, the magnitude of HbA1c reductions observed in DIA2003 with canagliflozin BID dosing was numerically smaller when compared to the same total daily dose of canagliflozin administered QD in DIA3006. As discussed in section 6.1.5, Analysis of Secondary Endpoints, the observed reductions in FPG with canagliflozin was also numerically smaller in DIA2003 compared to DIA3006, and the observed FPG reductions in DIA2003 with both canagliflozin groups were similar and did not demonstrate an incremental benefit with the higher dose of canagliflozin.

**Table 11: Change from Baseline in HbA1c to Primary Endpoint – Comparison of QD and BID Dosing**

Add-on to metformin Trials	Placebo	Canagliflozin 100 mg Total Daily Dose	Canagliflozin 300 mg Total Daily Dose
<b>BID dosing – DIA2003 (N)</b>	93	90	91
Baseline	7.66	7.63	7.53
LS Mean Change	-0.01	-0.45	-0.61
LS Mean Difference (95% CI)		-0.44 (-0.64,-0.25)	-0.60 (-0.79,-0.41)
<b>QD dosing – DIA3006 (N)</b>	181	365	360
Baseline	7.96	7.94	7.95
LS Mean Change	-0.17	-0.79	-0.94
LS Mean Difference (95% CI)		-0.62 (-0.76,-0.48)	-0.77(-0.91,-0.64)

The trial designs for DIA2003 and DIA3006 were similar with regard to study enrollment criteria, and the HbA1c criterion for study entry was 7 to 10.5% for both trials. However, the overall mean baseline HbA1c was lower in DIA2003 (7.6%) compared to DIA3006 (7.9%) despite similar inclusion criteria. About 22.2% subjects had baseline HbA1c <7% in DIA2003 compared to 12.5% in DIA3006. The applicant conducted a simulation (i.e., bootstrap simulation) to demonstrate that the observed differences in HbA1c-lowering with canagliflozin between these two trials were due to baseline differences in HbA1c. Please see the Statistical Review by Dr. Wei Liu for comments related to bootstrap simulation, but it should be noted that this is a post-hoc analysis to account for one of the variables noted between these two trials and not conclusive.

One of the main study differences between these two trials was the duration of the double-blind treatment period (18 weeks in DIA2003 compared to 26 weeks in DIA3006). However, the HbA1c reductions at Week 18 in DIA3006 were numerically similar to Week 26 results, and the placebo-adjusted LS mean changes in HbA1c from baseline to Week 18 was -0.56% and -0.73% with canagliflozin 100 mg and 300 mg QD respectively. Therefore, the magnitude of HbA1c lowering in DIA2003 remains smaller than DIA3006 at the same time point (Week 18).

**Reviewer’s comment: The HbA1c reductions observed in DIA2003 with BID dosing of canagliflozin were numerically smaller when compared to the same total daily dose of canagliflozin administered QD in DIA3006. DIA2003 and DIA3006 were similarly designed trials with analogous study enrollment criteria including HbA1c. The applicant attributed the observed differences in glycemic efficacy to baseline differences in HbA1c between the two trials, and conducted a post-hoc analysis using bootstrap simulation. However, post-hoc comparisons of efficacy across clinical trials have several limitations and can be confounded by many known and unknown factors. Therefore, the clinical data submitted in the FDC NDA have not demonstrated that BID administration of canagliflozin would provide similar glycemic control as QD administration of canagliflozin at the same total daily doses.**

## 7 Review of Safety

### **Safety Summary**

The safety data from a pooled dataset which included three placebo-controlled 26-week Phase 3 trials where canagliflozin was added to the background metformin therapy (referred to as DS1-M) was reviewed and also compared to a similar pooled dataset of four placebo-controlled 26-week Phase 3 trials from the canagliflozin NDA (referred to as DS1). No additional safety concerns were identified with combined use of canagliflozin and metformin compared to the individual components.

Canagliflozin was administered once daily in these Phase 3 trials, and in the FDC, the same total daily dose of canagliflozin is proposed to be administered twice daily due to the metformin IR component. A newly conducted Phase 2 trial (DIA2003) for the FDC provided safety data for co-administration of canagliflozin twice daily with metformin IR. The review of safety and tolerability from this trial demonstrated similar safety and tolerability to that of once daily administration of canagliflozin at the same total daily doses with metformin.

Therefore, the safety and tolerability of co-administration of canagliflozin and metformin twice daily as FDC would be expected to be similar to the individual components (i.e., canagliflozin NDA and Glucophage).

### **7.1 Methods**

The overall safety of canagliflozin was reviewed and discussed in the Clinical Review for NDA 204-042. The applicant also referenced Glucophage NDA for safety profile of metformin.

#### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

In support of the FDC, a pooled dataset that included three placebo-controlled 26-week trials evaluating the addition of canagliflozin to the background metformin therapy (alone or with another AHA) was used for the primary assessment of safety for combined use of canagliflozin with metformin. This will be referred to as DS1-M and include trials DIA3002, DIA3006, and DIA3012. This dataset was compared to a similar pooled dataset in the canagliflozin NDA that also included the placebo-controlled monotherapy trial (DIA3005) in addition to these 3 trials (referred to as DS1 in NDA 204-042) in order to assess possible differences in safety profile.

Of all the Phase 2 and 3 trials in support of this FDC, only DIA2003 was not previously reviewed in the canagliflozin NDA. Safety data from DIA2003 provide the only clinical data for twice daily administration of canagliflozin with metformin as proposed in the FDC. The overall safety data from DIA2003 were reviewed to assess whether there are

any differences in the safety profile between twice daily and once daily administration of canagliflozin at the same total daily doses with metformin.

In addition, data from the 4MSU were evaluated to update adverse event profile. Data from the 4MSU were presented when there were notable findings.

### **7.1.2 Categorization of Adverse Events**

Adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0. The grouping of MedDRA terms used to search for specific events (e.g., volume depletion, genital mycotic infections, etc) were same as the search terms used in the canagliflozin NDA.

### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

One pooled dataset of three Phase 3 trials were used to evaluate the safety related to combined use of canagliflozin with metformin, DIA3002, DIA3006, and DIA3012. This is referred to as DS1-M.

## **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

At the time of NDA submission, a total of 5151 subjects had received canagliflozin with background metformin therapy from all clinical trials in the Phase 3 program. Table 7 shows the overall exposure in subjects who were receiving metformin at baseline in all Phase 3 trials.

**Table 12: Overall Exposure in Subjects on Metformin at Baseline in all Phase 3 Trials**

	----- Number of Subjects -----			
	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana
Total Number of Subjects with Metformin at Baseline in Phase 3 Program	2392	2759	5151	2917
6-month Exposure	2172	2428	4600	2539
12-month Exposure	2009	2193	4202	2201
18-month Exposure	1158	1126	2284	1072
24-month Exposure	346	333	679	307

Note: The cutoff for studies DIA3002, DIA3006, DIA3012, and DIA3015 is end of the study.

The cutoff of the rest of the phase 3 studies (DIA3004, DIA3008, DIA3009, and DIA3010) is July 1, 2012.

A subject is counted in the 6-month, 12-month, 18-month and 24-month exposure if his/her duration of treatment is greater or equal to 24 weeks, 50 weeks, 76 weeks, and 102 weeks.

The summary is based on modified intent-to-treat set which included all randomized subjects that took at least one dose of study treatment.

Source: ISS-addendum, Table 4

The mean duration of exposure in DS1-M was 24 weeks in the canagliflozin groups compared to 22 weeks in the placebo group. The total subject exposure to canagliflozin was 590 subject-years before rescue. Overall, the subject exposure for DS1-M was very similar to DS1, which is not unexpected given that the only difference between the two pooled datasets is exclusion of one Phase 3 trial in DS1-M.

The mean duration of exposure in DIA2003 was 17 weeks in all the three treatment groups. The total subject exposure to canagliflozin was 60 subject-years in DIA2003.

At the time of 4-Month Safety Update for this FDC NDA with the data cutoff date of December 31, 2012, the total exposure to canagliflozin was 9436 subject-years, which represented about a 17% increase in the total exposure of subjects to canagliflozin compared to the 4MSU for canagliflozin NDA (which had a data cutoff date of July 1, 2012).

## 7.2.2 Explorations for Dose Response

The dose response exploration was discussed in my canagliflozin NDA review and Phase 3 trials evaluated canagliflozin dose of 100 mg and 300 mg daily. The proposed canagliflozin/metformin IR FDC doses are 50/500 mg, 50/1000 mg, 150/500 mg, and 150/1000 mg to be given twice daily with meals, due to the metformin IR component of the FDC. The applicant evaluated canagliflozin 50 mg and 150 mg twice daily added to the background metformin therapy in DIA2003.

## 7.2.3 Special Animal and/or In Vitro Testing

Please refer to Dr. Fred Alavi's review for full details.

## 7.2.4 Routine Clinical Testing

The applicant obtained laboratory tests, vital signs, and ECGs at appropriate time points during the treatment period in the DIA2003 trial. I reviewed the timing of clinical testing for Phase 3 trials in my canagliflozin NDA review, and found it adequate.

## 7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4.4 Clinical Pharmacology of this review as well as Dr. Ritesh Jain's review for full details. Also refer to the canagliflozin product labels for more information, including drug-drug interaction.

## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please refer to section 2.4 Important Safety Issues With Consideration to Related Drugs for a list of the labeled safety concerns with canagliflozin and metformin. The expected adverse events were adequately assessed in this FDC application, with appropriate updated information in the Four-Month Safety Update.

## 7.3 Major Safety Results

### 7.3.1 Deaths

Deaths in all Phase 3 trials were already discussed in NDA 204-042. One death was reported in the new Phase 2 trial, DIA2003, in one subject who received canagliflozin 150 mg BID:

**Colon cancer:** Subject 230105 was a 61-year-old man with past history of hypercholesterolemia, hypertension, cholecystectomy, and a family history of gastrointestinal cancer. During screening (24 days before baseline), he reported lower abdominal pain, which resolved. On Day 40, after receiving canagliflozin 150 mg BID, the CT scan of abdomen and pelvis showed possible colon carcinoma. The study drug was discontinued on Day 41. The histopathology report of the biopsy from Day 58 was positive for K-RAS mutation of malignant cells. On Day 243, he died due to colon cancer.

**Reviewer's comment: The latency of event (40 days) is too short for colon cancer to be causality related to the initiation of canagliflozin.**

### 7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events for all Phase 3 trials were already discussed in NDA 204-042.

Nonfatal serious adverse events were reported in two subjects from DIA2003, one of which also led to study discontinuation, and are briefly described below.

#### **Pyelonephritis, nephrolithiasis (these events also led to study discontinuation):**

Subject 230314 is a 58-year-old woman with an indwelling urinary catheter placed several years before study entry. Her urinalyses during screening and at baseline were positive for bacteria, blood, protein, leukocyte esterase, and nitrate. On Day 56 after starting canagliflozin 150 mg BID, she was taken to the emergency department because of several days of vomiting. She reported general weakness, fever, coughing, and throat pain for at least two weeks, and presented with fever, chills, rigors, dysuria, frequency, suprapubic and flank pain. Study drug was discontinued on Day 60. Urine culture on Day 64 was positive for candida albicans and urinalysis showed presence of leukocytes. She received antibiotics and ketoconazole. Other findings included progression of suspected abscesses in the retroperitoneum and in the tract of the kidney outflow system, and right side nephrectomy released purulent urine. CT examination showed abscessing pyelonephritis in the right kidney with lithiasis and purulent transudate in the retroperitoneum and fluid in abdominal cavity. On Day 65, nephrectomy was done with drainage of retroperitoneum and peritoneal cavity. Pathology and histology of kidney showed multiple renal stones, chronic pyelonephritis, and advanced atherosclerotic nephrosclerosis in all blocs of right kidney. On Day 78, Klebsiella pneumoniae and Enterococcus faecalis were found in the urine. Pyelonephritis and nephrolithiasis resolved on Day 91. She was withdrawn from study on Day 93.

**Reviewer's comment: Canagliflozin has been associated with decreases in serum urate levels, and nephrolithiasis is a potential adverse event of concern. Subject 230314 had risk factors for nephrolithiasis at baseline. In the overall canagliflozin program, the incidence of nephrolithiasis did not increase with canagliflozin.**

**Oroantral fistula, postoperative wound complication:** Subject 230449 is a 41-year-old woman with a past history of oroantral fistula, maxillary sinusotomy, and plasty of oroantral fistula, and active medical history of chronic maxillary sinusitis and chronic rhinitis. After starting canagliflozin 150 mg BID, she had viral respiratory tract infection and acute sinusitis on Day 17. She was treated, no action was taken with the study drug, and the events resolved by Day 29. On Day 35, she was hospitalized and underwent plasty due to oroantral fistula. She experienced postoperative wound complication. She continued the study drug, and events resolved on Day 52. She completed the study on Day 127.

### 7.3.3 Dropouts and/or Discontinuations

Adverse events leading to discontinuations for all Phase 3 trials were reviewed in NDA 204-042.

In DIA2003, the largest incidence of adverse events leading to discontinuation was seen in the canagliflozin 150 mg BID group (7.5% [7 subjects]), and the most common event leading to discontinuation was vulvovaginal pruritus in two female subjects as shown in Table 8. In one of these subjects (230104), vulvovaginal pruritus recurred once she restarted the study drug after resolution of the first episode, which ultimately led to study discontinuation.

Discontinuation due to colon cancer was discussed in Deaths (section 7.3.1; subject 230105), and discontinuation due to pyelonephritis and nephrolithiasis was discussed in Nonfatal Serious Adverse Events (section 7.3.2; subject 230314).

**Table 13: DIA2003 - Adverse Events (AEs) Leading to Study Discontinuation**

Preferred Terms	Canagliflozin 50 mg BID (N=93)	Canagliflozin 150 mg BID (N=93)	Placebo (N=93)
Total # of subjects with AEs	1	7	0
Vulvovaginal pruritus	0	2	0
Dermatitis Allergic	0	1	0
Palpitations	0	1	0
Pyelonephritis	0	1	0
GFR decreased	0	1	0
Nephrolithiasis	0	1	0
Colon cancer	0	1	0
Headache	1	0	0

GFR=glomerular filtration rate;

NOTE: One subject experienced two adverse events (pyelonephritis and nephrolithiasis) on study Day 60;

Source: CTR DIA2003, Table 26

Four remaining adverse events leading to discontinuation are summarized below.

**Glomerular filtration rate decreased:** Subject 230398 is a 74-year-old woman with a history of hydronephrosis, left renal cysts, chronic pyelonephritis, and nephrolithiasis who received canagliflozin 150 mg BID. Her baseline eGFR was 65 mL/min/1.73m<sup>2</sup>, and on Day 85, her eGFR decreased to 54 mL/min/1.73m<sup>2</sup>. An ultrasound performed on Day 91 to investigate hematuria showed pyelocaliectasis and left renal cyst. No treatment was given. Study drug was discontinued on Day 95 and she was withdrawn from the study on Day 98 due to decreased GFR. On follow-up (Day 101), decreased eGFR was not resolved (58 mL/min/1.73<sup>2</sup>).

**Dermatitis allergic:** Subject 230044, a 29-year-old woman without any prior history of allergies, reported acute allergic dermatitis 13 days after receiving canagliflozin 150 mg BID, characterized by severe redness of the skin, swelling of the lips, and slightly raised

rash “all over the body” associated with itching. No respiratory symptoms, other systemic symptoms or mucosal involvement were reported. She was treated with prednisone and hydroxyzine, study drug was discontinued on Day 19, and the event resolved on Day 22.

**Palpitation:** Subject 230097 is a 62-year-old smoking man with various past medical history which included obsessive-compulsive disorder, dyslipidemia, insomnia and discontinued the study drug due to palpitation on Day 2 after starting canagliflozin 150 mg BID. At baseline, he was in normal sinus rhythm, and ECG readings were normal at baseline and on Day 13.

**Headache:** Subject 052005, a 74-year-old woman with past history of hypertension and dyslipidemia, experienced headache and nausea on Day 16 after receiving canagliflozin 50 mg BID. She did not receive any treatment for her headache, the study drug was discontinued on Day 16, and she was subsequently withdrawn from the trial on Day 49 due to headache.

**Reviewer’s comment: Vulvovaginal pruritus, decreased GFR, and skin hypersensitivity reaction are labeled safety issues related to canagliflozin.**

### 7.3.4 Significant Adverse Events

Significant adverse events related to canagliflozin were discussed in NDA 204-042. Here, I will briefly summarize adverse events of interest observed in DIA2003 and at 4MSU.

#### DIA2003

No adverse events of myocardial infarction, stroke, hospitalized unstable angina, hospitalized congestive heart failure, venous thromboembolism, or fractures were reported. No volume depletion-related adverse events were reported. A higher incidence of subjects with osmotic diuresis-related events occurred in the canagliflozin 150 mg BID group (7.5% [7/93]) compared to none in canagliflozin 50 mg BID or placebo groups; these events were mild and none led to study discontinuation.

*Urinary Tract Infection:* The incidence of urinary tract infection (UTI) was slightly higher with canagliflozin, 4% [4/93] in each canagliflozin group compared to 2.2% [2/93] in the placebo group. Only one serious adverse event of upper UTI with canagliflozin 150 mg BID was reported (discussed in the Nonfatal Serious Adverse Events, section 7.3.2).

*Genital Mycotic Infection:* One subject in the canagliflozin 50 mg BID group and one subject in the placebo group reported an adverse event of male genital mycotic infection. Female genital mycotic infections were reported in 11.3% (6/53) and 8.2% (4/49) with canagliflozin 50 mg and 150 mg BID respectively, compared to 4.3% (2/47)

with placebo. Two subjects who experienced vulvovaginal pruritus after receiving canagliflozin 150 mg BID discontinued the study (section 7.3.3).

**Hypoglycemia:** The incidence of biochemically documented hypoglycemia (i.e., glucose  $\leq 70$  mg/dL with or without symptoms) was low, with 4.3% (4/93) and 3.2% (3/93) in the canagliflozin 50 mg and 150 mg BID groups respectively compared to 3.2% (3/93) in the placebo group. Only one subject who received 50 mg BID reported fingerstick glucose  $< 56$  mg/dL during two episodes without any accompanying clinical symptoms. No severe hypoglycemia was reported.

#### 4MSU

At 4MSU, no new trends or patterns of deaths, serious adverse events, or adverse events leading to discontinuations were identified with canagliflozin. No new hepatic cases meeting biochemical Hy's law criteria were identified.

**Fractures:** The updated incidence of fracture data again demonstrated a higher incidence of all fractures, adjudicated fractures, and adjudicated low trauma fractures with canagliflozin compared to the non-canagliflozin group (Table 14). In this updated data, the 95% CI for the between-group differences for all fractures and adjudicated low trauma fractures excluded 0 for comparison of all canagliflozin versus non-canagliflozin groups. Similarly, a higher incidence of adverse events of upper limb fractures was seen with canagliflozin group (1% with all canagliflozin versus 0.6 with all non-canagliflozin groups).

**Table 14: Post Radnomization Fracture Adverse Events - Regardless of Rescue Therapy - Through December 31, 2012**

Fracture Type	Canagliflozin 100 mg (N=3092)	Canagliflozin 300 mg (N=3085)	All Canagliflozin (N=6177)	All Non-Canagliflozin (N=3262)	Canagliflozin 100 mg Minus All Non-Canagliflozin		Canagliflozin 300 mg Minus All Non-Canagliflozin		All Canagliflozin Minus All Non-Canagliflozin	
	n (%)	n (%)	n (%)	n (%)	Diff <sup>a</sup>	95%CI <sup>b</sup>	Diff <sup>a</sup>	95%CI <sup>b</sup>	Diff <sup>a</sup>	95%CI <sup>b</sup>
<b>Total no.subjects with adverse events<sup>c</sup></b>	87 (2.8)	91 (2.9)	178 (2.9)	64 (2.0)	0.9	( 0.1; 1.6)	1.0	( 0.2; 1.8)	0.9	( 0.3; 1.6)
Incidence rate per 1,000 person-years exposure (SE) <sup>d</sup>	18.26 (1.97)	19.48 (2.05)	18.86 (1.42)	13.74 (1.73)	4.5	(-0.63; 9.65)	5.7	( 0.47; 11.00)	5.1	( 0.73; 9.51)
<b>Total no. subjects with Adjudicated Fracture Type<sup>e</sup></b>	78 (2.5)	72 (2.3)	150 (2.4)	58 (1.8)	0.7	(-0.0; 1.5)	0.6	(-0.2; 1.3)	0.7	( 0.0; 1.3)
High Trauma	16 (0.5)	14 (0.5)	30 (0.5)	13 (0.4)	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	60 (1.9)	57 (1.8)	117 (1.9)	41 (1.3)	0.7	( 0.0; 1.3)	0.6	(-0.1; 1.2)	0.6	( 0.1; 1.2)
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)

<sup>a</sup> Denotes the difference in the incidence rate or the difference in proportion of subjects with the adverse event

<sup>b</sup> CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

<sup>c</sup> Fracture adverse events based upon a prespecified subset of preferred terms from a MedDRA query listed in the SAP.

<sup>d</sup> Exposure adjusted incidence rates are per 1,000 person-years and calculated as  $1,000 \times (\text{total number of subjects with at least one specified event} / \text{total person-year exposure for all safety subjects in each treatment group})$ . 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.

<sup>e</sup> 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.

Source: NDA 204-353, 4MSU, Table 11

*Malignancies:* There were no events of pheochromocytoma or Leydig cell tumors through December 31, 2012.

There were an additional 1, 2, and 2 subjects with bladder cancer in the canagliflozin 100 mg, 300 mg, and non-canagliflozin groups respectively in this 4MSU; the incidence rate per 1000 person-years was 0.64 and 0.86 in the combined canagliflozin and non-canagliflozin groups respectively.

There were an additional 1, 2, and 1 subject with breast cancer in the canagliflozin 100 mg, 300 mg, and non-canagliflozin groups respectively in this 4MSU; the incidence rate per 1000 person-years was 3.76 and 3.37 in the combined canagliflozin and non-canagliflozin groups respectively.

There were an additional 1 and 2 subjects with renal cancer in the canagliflozin 300 mg and non-canagliflozin groups respectively in this 4MSU; the incidence rate per 1000 person-years was 0.53 and 0.43 in the combined canagliflozin and non-canagliflozin groups respectively.

**Reviewer's comment: My review of adverse events in the DS1-M dataset did not identify any difference in the safety and tolerability of canagliflozin when added to metformin, compared to the overall canagliflozin adverse event profile per NDA 204-042. Similarly, my review of safety data from DIA2003 did not show any different patterns of safety issues when canagliflozin is administered twice daily in combination with metformin, compared to the safety data established where canagliflozin is given once daily. Also, my review of the 4MSU showed a similar adverse event profile to what was observed in the canagliflozin NDA.**

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The overall incidence and pattern of common adverse events was similar in the DS1-M as DS1.

In DIA2003, the most commonly reported adverse events were urinary tract infection (4.3% [4/93] and 3.2% [3/93] with canagliflozin 50 mg and 150 mg BID respectively compared to 2.2% [2/93] with placebo), headache (4.3% [4/93] and 2.2% [2/93] with canagliflozin 50 mg and 150 mg BID respectively compared to none with placebo), and pollakiuria (4.3% [4/93] with canagliflozin 150 mg BID compared to none with other treatment groups).

## 7.4.2 Laboratory Findings

The overall trends and changes in laboratory values were similar in the DS1-M compared to DS1.

In DIA2003, the following small differences with canagliflozin compared to placebo in the mean changes for laboratory values were observed from baseline to Week 18, and were consistent with the mean changes seen in the canagliflozin program (NDA 204-042):

- Increases in serum bilirubin in all treatment groups, 7.3% and 11.1% with canagliflozin 50 mg and 150 mg BID respectively compared to 5.4% with placebo;
- Increase in BUN was 11.3% and 14.3% with canagliflozin 50 mg and 150 mg BID respectively compared to 2% with placebo;
- Small increase in serum creatinine, 1.8% and 4.7% with canagliflozin 50 mg and 150 mg BID respectively compared to 1.4% with placebo; this corresponded to small decreases in eGFR, -0.7% and -3.8% with canagliflozin 50 mg and 150 mg BID respectively compared to -0.3% with placebo;
- Increase in serum magnesium of 7.2% and 8.6% with canagliflozin 50 mg and 150 mg BID respectively compared to 0.8% with placebo;
- Increase in serum phosphate of 5% and 7.9% with canagliflozin 50 mg and 150 mg BID respectively compared to 1.3% with placebo;
- Moderate decrease in serum urate, -13% and -11.2% with canagliflozin 50 mg and 150 mg BID respectively compared to -0.2% with placebo.

In DIA2003, the between-group differences chemistry values meeting PDLC criteria were small and not significant (see Table 35 of Clinical Study Report DIA2003).

## 7.4.3 Vital Signs

The mean changes from baseline in SBP, DBP, and pulse rate for DS1-M were overall similar to DS1 in the canagliflozin NDA.

In DIA2003, the mean reductions from baseline in SBP at Week 18 were -3.4 mmHg and -2.6 mmHg with canagliflozin 50 mg and 150 mg BID compared to an increase of 3 mmHg with placebo. The mean reductions from baseline in DBP at Week 18 were -1.8 mmHg and -1.6 mmHg with canagliflozin 50 mg and 150 mg BID compared to an increase of 1.1 mmHg with placebo. This was associated with a slight increase in the pulse rate, 0.9 and 1.4 bpm with canagliflozin 50 mg and 150 mg BID compared to no change with placebo.

**Reviewer's comment: The changes in vital signs observed in DIA2003 were within the range of changes observed in Phase 3 trials of canagliflozin in NDA 204-042.**

#### **7.4.4 Electrocardiograms (ECGs)**

The applicant had previously conducted cardiac electrophysiology study, and canagliflozin was found to have minor effects, if any, on ECG parameters in NDA 204-042. No significant ECG changes were observed in DIA2003.

#### **7.4.5 Special Safety Studies/Clinical Trials**

The applicant submitted 52-week results of the special safety study to evaluate the bone safety in elderly, DIA3010. The 52-week results were submitted and reviewed in NDA 204-042.

#### **7.4.6 Immunogenicity**

Not applicable as canagliflozin and metformin are not proteins and therefore not expected to be immunogenic.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

Dose dependency for adverse events related to canagliflozin was reviewed in NDA 204-042, and was noted for volume-depletion events, changes in renal function and renal adverse events. Previous clinical experiences with metformin have demonstrated that gastrointestinal adverse events such as nausea, abdominal pain, and diarrhea are related to dose.

#### **7.5.2 Time Dependency for Adverse Events**

Time dependency for adverse events related to canagliflozin was reviewed in NDA 204-042, where it was noted that most adverse events appear to occur early after treatment initiation, within 2-3 months. These included hypersensitivity-related skin reactions, volume depletion events, renal function changes, mycotic infections, fractures, and electrolyte changes. Previous experiences with metformin have shown that gastrointestinal adverse events occur upon initiating metformin, and tolerance develops over time.

#### **7.5.3 Drug-Demographic Interactions**

The drug-demographic interactions for the FDC are expected to be similar to the individual components. As noted in my review for NDA 204-042, subjects with reduced

renal function and elderly were at an increased risk for volume depletion-related adverse events and higher incidence of upper extremity fractures were noted in women.

#### **7.5.4 Drug-Disease Interactions**

The drug-disease interactions for the FDC are expected to be similar to the individual components. As noted in my review for NDA 204-042, the efficacy of canagliflozin depends on renal function and its efficacy is modest in those with moderate renal function. As noted in canagliflozin labeling, canagliflozin has not been studied and should not be used in those with severe renal impairment (e.g.,  $\leq 30$  mL/min/1.73m<sup>2</sup>), ESRD, or on dialysis. In addition, subjects with moderate renal impairment experienced more significant changes in renal function and had more renal-related events, and canagliflozin is to be discontinued in patients with eGFR  $< 45$  mL/min/1.73m<sup>2</sup>.

Subjects with renal impairment will be at a higher risk for lactic acidosis when receiving metformin therapy, as noted in the metformin labeling. Metformin is contraindicated in patients with renal function (e.g., serum creatinine  $\geq 1.5$  mg/dL in males and  $\geq 1.4$  mg/dL in females, or abnormal creatinine clearance). Metformin should also be avoided with hepatic insufficiency because of the risk for lactic acidosis.

#### **7.5.5 Drug-Drug Interactions**

Canagliflozin and metformin have not shown to have clinically relevant drug-drug interactions in two canagliflozin-metformin drug-drug interaction studies (NAP1004 and DIA1028), and thus is not expected to have any significant interactions with when co-administered as a FDC. NAP1004 and DIA1028 studies were reviewed in canagliflozin NDA; please see Dr. Vaidyanathan's review for canagliflozin NDA.

Please see the canagliflozin and metformin labeling for a complete drug-drug interactions expected with each individual product.

### **7.6 Additional Safety Evaluations**

#### **7.6.1 Human Carcinogenicity**

Nonclinical data suggest an increased risk for renal tubular tumors, pheochromocytomas, and Leydig cell tumors with canagliflozin. The incidence of malignancies was not increased with canagliflozin treatment with or without metformin as of December 31, 2012.

### **7.6.2 Human Reproduction and Pregnancy Data**

Canagliflozin is Pregnancy Category C. Rat studies have shown that canagliflozin may affect renal development and maturation where drug exposure occurred during animal development that corresponds to the late second and third trimester of human development. Canagliflozin has not been studied in pregnant women or nursing mothers.

Metformin is Pregnancy Category B, since there are no adequate and well-controlled studies of pregnant women with metformin.

As noted in Dr. Alavi's review, co-administration of canagliflozin and metformin to pregnant rats was neither embryolethal nor teratogenic.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

Studies in pediatric patients have not been performed. The applicant is proposing a partial waiver for pediatric studies in those less than 10 years of age, and deferral in those 10 to <18 years of age.

The applicant proposed that the two trials that are required to satisfy Pediatric Research Equity Act (PREA) Post-Marketing Requirements under canagliflozin NDA fulfill the PREA requirements for this canagliflozin/metformin FDC:

- A Phase 1, open-label, multiple oral dose study to evaluate the PK, PD, and safety of canagliflozin in older children and adolescents 10 to <18 years of age with T2DM and currently on a stable dose of metformin;
- A Phase 3, 26-week, randomized, double-blind, placebo-controlled, parallel group, multicenter trial, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy, safety, and tolerability of canagliflozin in the treatment of older children and adolescents (10 to <18 years of age) with T2DM, as add-on to metformin and as monotherapy (at least 30% of patients).

The applicant also proposed to conduct a swallowability study with the FDC tablet as the size is larger than currently available individual tablets.

The applicant's pediatric plan was discussed at the PeRC meeting on October 23, 2013, and was found to be acceptable by the Committee.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

No overdose, potential for abuse, or withdrawal and rebound were noted for canagliflozin.

## **7.7 Additional Submissions / Safety Issues**

## **8 Postmarket Experience**

## 9 Appendices

### 9.1 Literature Review/References

Relevant references are cited within relevant sections of this clinical review.

### 9.2 Labeling Recommendations

On April 26, 2013, the applicant submitted a labeling amendment to harmonize the labeling for the canagliflozin/metformin IR FDC with the final canagliflozin labeling approved on March 29, 2013. In addition, the applicant added the following two sentences to Section 6.1, under Laboratory Tests, Increases in Serum Potassium:

*In pooled data from four placebo-controlled trials, the mean change in serum potassium levels was 0.5% and 1.0% with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to 0.6% with placebo. Episodes of elevated serum potassium (greater than 5.4 mEq/L and 15% above baseline) were seen in 4.4% of patients treated with canagliflozin 100 mg, 7.0% of patients treated with canagliflozin 300 mg, and 4.8% of patients treated with placebo.<sup>1</sup>*

And the applicant provided the following rationale for their proposed addition:

*<sup>1</sup>The Warnings and Precautions section of the Invokana (canagliflozin) USPI states that “INVOKANA can lead to hyperkalemia”. However, the only potassium data in the INVOKANA USPI for the single agent is for subjects in clinical trial DIA3004 (patients with moderate renal impairment). As a result, frequent requests from healthcare providers for potassium data for subjects without renal impairment in the prescribing information have been received by the Sponsor. Therefore, the Sponsor requests including potassium data from the placebo controlled dataset (DS1) in Section 6.*

This is acceptable.

I do not have any further labeling recommendations at this time, as I do not recommend the approval of this NDA without a well-established plasma canagliflozin exposure-HbA1c response relationship.

### 9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not convened.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HYON J KWON  
10/31/2013

ALI MOHAMADI  
11/01/2013

## MEMORANDUM

Filing Meeting: January 24, 2013

NDA 204353

Drug: Canagliflozin/Metformin Immediate Release Fixed Dose Combination oral tablets

Sponsor: Janssen Pharmaceuticals, Inc.

Clinical Reviewer: Hyon J. Kwon, PharmD, MPH

Date received: December 12, 2012

PDUFA date: December 12, 2013

### Assessment:

From the clinical standpoint, the NDA is fileable.

### Background:

Janssen Pharmaceuticals, Inc. developed a fixed dose combination (FDC) tablets containing canagliflozin, a SGLT2 inhibitor, and metformin hydrochloride immediate release (IR). The proposed doses of canagliflozin/metformin IR FDC are 50/500, 50/1000, 150/500, and 150/1000 mg to be given twice daily for treatment of type 2 diabetes mellitus.

This is a 505(b)(2) application, and relies on data submitted in the canagliflozin NDA 204042 and in the Glucophage NDA 20357. Canagliflozin was filed on May 31, 2012, and is currently under review with PDUFA goal date of March 31, 2013.

The applicant proposes to use this FDC tablet in patients with inadequate glycemic control on a regimen containing canagliflozin or metformin, or in those patients already on metformin and canagliflozin dosed as separate tablets.

In the canagliflozin NDA 204042, the efficacy and safety of canagliflozin added to ongoing treatment with metformin (alone or with another AHA) was evaluated in the following Phase 2 and Phase 3 trials:

- Phase 2b, add-on to metformin dose-ranging study (DIA2001)
- Six Phase 3 studies which included: 2 studies in subjects on a defined metformin therapy alone (DIA3006 and DIA3009); 3 studies in subjects on metformin in combination with another AHA (DIA3002, DIA3012, and DIA3015); and one in subjects on insulin and metformin (DIA3008 Insulin Substudy, Population 3)
- Supportive data from DIA3010, Older Adults Study, since 85% of canagliflozin subjects were taking concomitant metformin (alone or in combination with other AHA).

Phase 3 trials under NDA204042 evaluated canagliflozin doses of 100 mg and 300 mg daily. Canagliflozin/metformin IR FDC is to be given twice daily due to metformin IR posology.

In order to bridge the results from canagliflozin NDA 204042 (100 mg and 300 mg daily) to support the canagliflozin/metformin IR FDC (50 mg and 150 mg twice daily), following are submitted in this FDC application:

- Four Phase 1 bioequivalence studies comparing to-be-marketed canagliflozin/metformin IR FDC tablet to the individual components (DIA1046, DIA1050, DIA1051, and DIA1038)
- A Phase 1 food effect study (DIA1037) with to-be-marketed 150/1000 mg of canagliflozin/metformin IR FDC
- A Phase 1 PK/PD study that compared once-daily versus twice daily administration of canagliflozin (DIA1032); this was also previously submitted under NDA 204042
- A Phase 1 relative bioavailability study comparing the canagliflozin/metformin IR FDC tablets to coadministration of individual components (DIA1036)
- A Phase 2, 18-week study in T2DM (DIA2003) comparing the efficacy and safety of twice daily administration of canagliflozin (50 mg and 100 mg BID) to placebo as add-on to metformin

The adequacy of bridging will be a review issue.

In addition, the applicant submitted a pooled safety analysis of three 26-week placebo-controlled studies where canagliflozin was added to metformin (DIA3002, DIA3006, DIA3012).

The applicant also submitted 52-week bone biomarker and bone density data from DIA3010, and a revised version of the 4-Month Safety Update previously submitted to the canagliflozin NDA 204042.

## CLINICAL FILING CHECKLIST FOR NDA

**NDA/BLA Number: 204353**

**Applicant: Janssen Research & Development, LLC**      **Stamp Date: December 12, 2012**

**Drug Name:**  
**Canagliflozin/Metformin IR FDC**  
**tablets**

**NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			In the Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2); canagliflozin (NDA 204042) and metformin (Glucophage, NDA 20357)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: DIA2001 Study Title: 28431754DIA2001	x			

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	Sample Size: 451 Location in submission: Module 5.3.5.1				
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1  Indication:  Pivotal Study #2  Indication:	x			4 Phase 1 BE studies; a Phase 1 food-effect study; a Phase 1 BA study; a Phase 1 PK/PD study for comparison of once daily compared to twice daily; a Phase 2b add-on to metformin dose-ranging study; a Phase 2 efficacy/safety study with twice daily canagliflozin as add-on to metformin; 6 Phase 3 studies of canagliflozin as add-on to metformin
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	Addressed in canagliflozin NDA 204042
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	x			A total of 5658 subjects with T2DM received canagliflozin and metformin; of these, 4600 were exposed to 6 months, and 4202 for 12 months.

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	x			Adverse events coded using the MedDRA version 14.0 or 14.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Narratives for SAEs and discontinuations provided in individual CSRs previously under canagliflozin NDA 204042; SAEs and discontinuation for DIA2003 provided
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			Yes from clinical standpoint, otherwise defer to other disciplines
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Requesting a waiver for pediatric studies in children <10 years of age, and deferral for 10 to <18 years of age
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		x		
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the			x	

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	raw data needed to derive these endpoints included?				
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			Sponsor requested and was granted waiver of IRB requirements under 21 CFR Part 56 for use in a foreign investigational study or all foreign investigational studied under IND 76,479

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_Yes\_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**None.**

Hyon J. Kwon, PharmD, MPH

\_\_\_\_\_  
Reviewing Medical Officer

\_\_\_\_\_  
Date

Jean-Marc Guettier, MD

\_\_\_\_\_  
Clinical Team Leader

\_\_\_\_\_  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HYON J KWON  
02/08/2013

JEAN-MARC P GUETTIER  
02/10/2013