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RESEARCH**

APPLICATION NUMBER:

204353Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	July 2, 2014
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204353
Cycle 2 resubmission	
Applicant	Janssen Research and Development, LLC
Date of Submission	10 Feb 2014
PDUFA Goal Date	10 Aug 2014
Proprietary Name / Established (USAN) names	Invokamet (canagliflozin/metformin HCl)
Dosage forms / Strength	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
Proposed 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
Recommended:	Approval

Cross Discipline Team Leader Review

1. Introduction

Invokamet is a proposed fixed-dose combination (FDC) tablet that contains two anti-diabetic medications: canagliflozin and metformin (immediate release formulation).

The current application is a 505(b)(2) resubmission for approval of the Invokamet 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.

Reference products: 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.

The first cycle (original) NDA was submitted 21 Dec 2012. This is a second cycle resubmission Complete Response letter (CRL) issued 12 Dec 2013 for the first cycle. Other details of the regulatory history are contained in Section 2 (Background).

The critical review elements for this resubmission are contained in Section 5 (Clinical Pharmacology). Issues from this discipline comprised the reasoning for the CRL, as discussed below. In this resubmission, there is no new pertinent information for CMC, nonclinical pharmacology/toxicology, clinical efficacy or safety.

2. 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 FDC drug product is dosed twice daily with the following proposed dosage strengths (canagliflozin/metformin): 50 mg/500 mg, 50 mg/1000 mg, 150 mg/500 mg, and 150 mg/1000 mg. As noted in Dr. Guettier's original cycle review, this twice daily dosing frequency differs from the dosing frequency of the single entity canagliflozin product, i.e. once daily. However, the twice daily dosing frequency of metformin hydrochloride in the Invokamet FDC product is the same as the dosing frequency of the single entity metformin hydrochloride product.

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). These trials demonstrated that addition of canagliflozin to a stable maximally effective dose of metformin improves glycemic control in subjects with type 2 diabetes.

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 in the original NDA, the sponsor sought to bridge QD and BID dosing of canagliflozin with an approach that included 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.

During the NDA review, inadequacies were found in the sponsor's plan to bridge the once- and twice daily canagliflozin doses (described fully in the Clinical Pharmacology review). In brief, the sponsor failed to demonstrate an exposure-response relationship for canagliflozin, as patients who receive canagliflozin QD appeared to have superior clinical efficacy with those patients receiving the same daily dose BID. Specifically, a cross-trial comparison showed that the efficacy (placebo-subtracted change from baseline in HbA1c) was lower in canagliflozin BID dosing regimen (-0.44% and -0.60% with 50 and 150 mg BID doses) compared to efficacy observed in the QD regimens (-0.59% and -0.67% with 100 and 300 mg QD doses) in earlier conducted Phase 3 trial (NDA 204042). The Sponsor did submit data from a Phase 2 study (DIA 2003) that evaluated the efficacy (change from baseline in HbA1c at week 18) of 50 mg and 150 mg BID of canagliflozin as an add-on to stable doses of metformin against placebo in T2DM patients who were inadequately controlled on metformin. However, the sponsor did not include the corresponding QD regimens and thus could not establish that BID regimen resulted in similar efficacy as the QD regimen. Finally, the sponsor's bioequivalence studies rely upon PD markers that have not been validated as surrogates for clinical efficacy in type 2 diabetes mellitus (T2DM).

The Sponsor was informed of FDA's concerns related to the bridging issue at the time of the Mid-Cycle meeting (see Mid-Cycle Communication Letter issued on 6 Jun 2013), as well as at the Late-Cycle meeting on 12 Sep 2013 (see Late-Cycle Meeting Minutes finalized 26 Sep 2013).

FDA issued a CRL on 12 Dec 2013 because the clinical and clinical pharmacology data submitted to support approval were insufficient to bridge QD and BID dosing of canagliflozin. See CLR dated 11 Dec 2013, Primary Clinical Review dated 1 Nov 2013, Clinical Pharmacology Review dated 15 Nov 2013, Cross-Discipline Team Leader Review dated 10 Dec 2013, and Division Director memo dated 30 Nov 2013 for details.

Excerpted from the CR letter:

1. The clinical and clinical pharmacology data submitted to support approval of the application are insufficient to allow reliance on the efficacy findings from NDA 204042, evaluating canagliflozin dosed once-daily, to support approval of the canagliflozin and metformin fixed dose combination product due to the following deficiencies.

a. Data supporting the existence of a robust relationship between plasma canagliflozin concentration and hemoglobin A1c (HbA1c) reduction is lacking.

b. Your Phase 1 study (DIA1032) is not sufficient to bridge efficacy findings between canagliflozin dosed once daily with canagliflozin dosed twice daily. You have not provided data demonstrating a robust relationship between the PD marker used in DIA1032 [i.e., Urinary Glucose Excretion/Renal Threshold for Glucose Excretion (UGE/RTG)] and HbA1c reduction. In the absence of these data, UGE/RTG cannot be used to predict long-term HbA1c response. Canagliflozin binds both SGLT-1 and SGLT-2 and the totality of its glucose lowering effect may not be fully captured using a PD marker relying solely on renal glucose handling. In PK/PD study NAP1002 for example, saturation of the UGE effect was seen at the 100 mg dose yet in efficacy trials the 300 mg dose was shown to afford further glucose lowering.

c. The bootstrap method to bridge findings between DIA2003 and DIA3006 cannot be used to address the above listed deficiencies.

In order to address these deficiencies, you will need to bridge the efficacy of canagliflozin when the daily dose is administered once-daily to the efficacy of canagliflozin when the daily dose is administered twice-daily using a robust modeling and simulation strategy. We recommend you seek FDA guidance regarding model development. If you cannot generate a robust model with the data you have on hand, you will need to compare the efficacy of once-daily and twice-daily dosing of canagliflozin head to head in a clinical trial.

FDA also met with the Sponsor to discuss their modeling and analysis plan on 19 Dec 2013 (see minutes 15 Jan 2014), and provided advice on the applicant's modeling strategy. General agreement was reached on the Sponsor's modeling and analysis plan, which was to include a dynamic population PK/PD analysis on the effect of QD vs. BID dosing regimens on the exposure-response relationship of canagliflozin on HbA1c, with the following issues outstanding:

- 1. The Agency reiterated that any comments on the design of non-inferiority virtual trial simulation will be communicated to the applicant after an internal meeting with statistics and clinical.*
- 2. The Agency recommended that the data relevant for estimating the magnitude of gut effect should be included in the package at the time of NDA submission.*

The following advice was provided in a letter dated 24 Jan 2014.

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

3. CMC/Device

This submission does not contain any new chemistry/manufacturing/controls data. During the first cycle review, 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 (dated 28 Oct 2013). 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 (review dated 16 Jul 2013).

4. Nonclinical Pharmacology/Toxicology

For the original submission, nonclinical pharmacology and toxicology data were found to support approval of NDA 204353 and are detailed in Dr. Alavi’s review.

For the resubmission Dr. Alavi has the same recommendation, i.e. approval. He notes that the CRL contained no nonclinical deficiency and the resubmission contains no new pivotal nonclinical studies. The resubmission, however, contains several amendments and minor pharmacokinetic studies previously submitted to canagliflozin (NDA 204042) and original CanaMet-IR FDC NDA 204353. The amendments and minor studies contain no new information pertinent to the approval decision or label. For details please see Dr. Alavi’s review dated 10 Jun 2014.

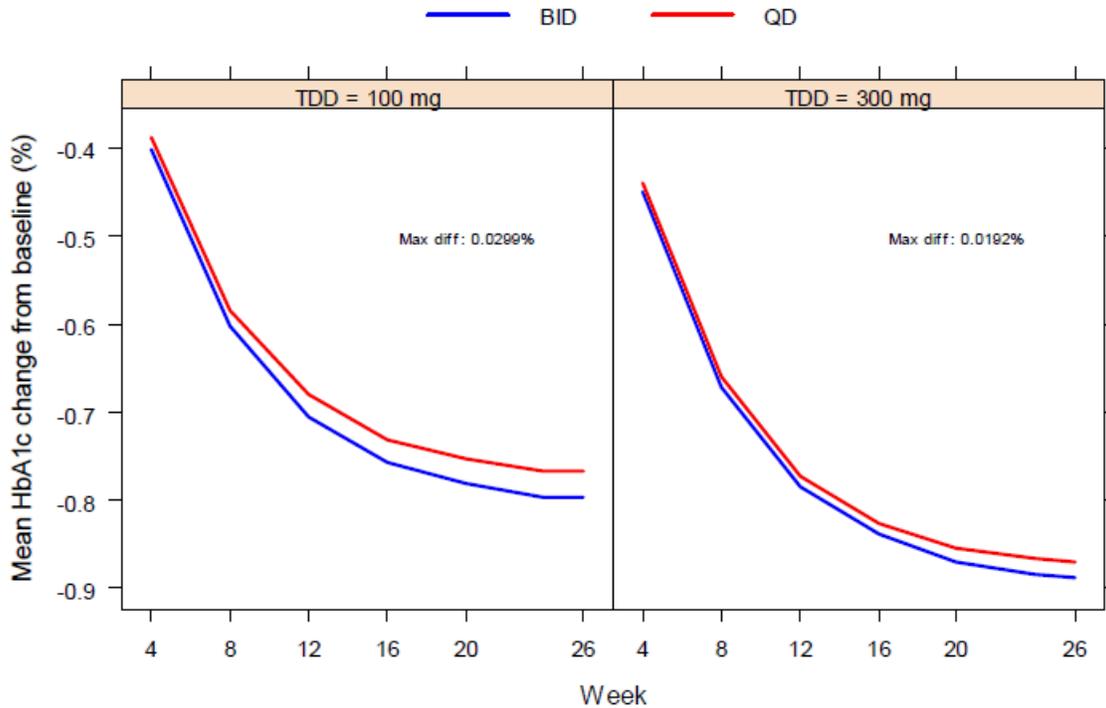
5. Clinical Pharmacology/Biopharmaceutics

The Pharmacometrics reviewer Dr. Anshu Marathe and the Clinical Pharmacology reviewer Dr. Ritesh Jain (both from the Office of Clinical Pharmacology [OCP]) recommended approval of this NDA (see review dated 20 Jul 2014). As noted in section 2 (Background), the primary reason for the first cycle CR was inability to bridge the once- and twice daily canagliflozin doses.

This section summarizes the findings of the OCP reviewers in support of approval of this NDA.

The OCP reviewers concluded that the population PK-PD model developed and performed by the Sponsor adequately bridges the efficacy of canagliflozin from once-daily administration (QD) to twice-daily administration (BID). The Sponsor’s simulation using population PK and exposure-response models (under similar baseline covariate values, including HbA1c, the

same study effect), demonstrated that HbA1c change from baseline for BID and QD dosing regimens are fairly similar. The figure below from the OCP review shows the simulated mean HbA1c change from baseline profiles for total daily doses of 100 mg and 300 mg administered as QD and BID regimens. 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 a slightly greater HbA1c reduction. These small differences are not considered clinically meaningful.



Note: Max diff=maximum difference in mean HbA_{1c} change from baseline up to Week 26 between QD and BID dosing for the same TDD.

Key: BID=twice daily; QD=once daily; HbA_{1c}=glycated hemoglobin; TDD=total daily dose

The OCP review also concluded that the model addresses Agency's question that the 300 mg QD dose could have an additional effect on HbA1c lowering through the SGLT-1 pathway, i.e. besides the SGLT-2 pathway. See section 2.1.4 of the OCP review for details. The model data as well as other experimental data that included fasting plasma glucose comparisons between dosing regimens suggested that the additional HbA1c lowering effect for the 300 mg QD dose was not significantly driven by SGLT-1 inhibition.

The OCP review also notes that an inspection by DSI (Division of Scientific Investigation) was requested for the pivotal BE study (DIA 1038) and Phase 1 PK/PD study (DIA1032) in the previous cycle. The outcome of the inspection was not captured in the review during the first cycle. The inspection concluded that the clinical and analytical portions of these studies are acceptable and data from these studies are acceptable to be used for Agency's review. Please refer to the DSI review by Dr. Dasgupta in DARRTs dated 0/17/2013 for further details.

6. Clinical Microbiology

Not applicable to this NDA

7. Clinical/Statistical- Efficacy

There is no new efficacy information for this resubmission. Please see Dr. Kwon's primary clinical review for the second cycle (23 Jul 2014), Dr. Ali Mohamadi's Cross Discipline Team Leader memo from the first cycle (10 Dec 2013) and Dr. Jean-Marc Guettier's Division Director memo (30 Nov 2013) from the first cycle dated for a discussion of efficacy.

Table 1 shows the trials reviewed in support of this NDA.

Table 1: Trials Supporting the Canagliflozin+metformin IR FDC

Trial	Trial Design	Trial Population	Treatment Arms: # of Subjects Randomized	Duration
Trials supporting Efficacy and Safety				
Phase 2 Trials				
DIA2001 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
DIA2003 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
Phase 3 Trials				
DIA3006^a 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]
DIA3009 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)
DIA3002 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)
DIA3012^a 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]
DIA3015 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
DIA3008 Insulin Substudy (Population 3) Add-on to insulin + metformin	Randomized, double-blind, placebo-controlled, parallel group	T2DM subjects on insulin ≥ 30 units/day + metformin ≥ 2000 mg/day; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 139 Cana 300 mg: 148 Placebo: 145	18 weeks
Trials supporting the review of safety only, i.e. controlled extensions				
DIA3010 Older Adults	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)
DIA3014*	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

*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: Dr. Kwon's review

8. Safety

Safety data were reviewed in detail by Dr. Kwon for this sNDA (23 Jul 2014). The new safety information since the original NDA submission included data from (see Table 1):

1. Controlled extension data from DIA3009
2. DIA3014
3. Controlled extension data from DIA3010
4. 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.

Based on review of these data, Dr. Kwon did not note any new safety issues that have not already been identified in the original NDA submission. Please see her review for details.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this sNDA.

10. Pediatrics

The proposed pediatric study plan was reviewed by the pediatric review committee on October 23, 2013. At that time, the pediatric review committee was in agreement with the study plan, which is the same as planned for the single entity canagliflozin pediatric drug development plan. In other words, 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.

Because of the large size of the canagliflozin+ metformin IR tablet, further discussions with PeRC regarding swallowability study led to the recommendation of a swallowability study. Therefore, a PREA required study will be 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.

11. Other Relevant Regulatory Issues

None identified

12. Labeling

A line-by-line labeling reviewed will be conducted separately.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

I agree with the recommendations from the Office of Clinical Pharmacology that the modeling and simulation strategy with exposure – response analysis was satisfactorily utilized to adequately bridge efficacy between QD and BID dosing regimens for canagliflozin to support approval of canagliflozin/metformin fixed dose combination (FDC) product for treatment of adult patients with type 2 diabetes. Exposure-response analysis demonstrated that the efficacy of canagliflozin is similar following QD or BID dosing regimen.

Cross Discipline Team Leader Review

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

See Pediatrics above

- Recommended Comments to Applicant

Labeling comments will be communicated to the applicant separately.

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/s/

LISA B YANOFF
08/07/2014

JEAN-MARC P GUETTIER
08/08/2014
I concur.