CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205879
Supporting document/s:	000
Applicant's letter date:	Nov 20, 2015
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Product:	Canagliflozin + metformin XR (INVOKAMET® XR)
Indication:	Type 2 diabetes
Applicant:	Janssen Pharmaceuticals Inc.
Review Division:	DMEP
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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability: Nonclinical data supports the approval of NDA 205879

1.1.2 Additional Nonclinical Recommendations: No new nonclinical studies are recommended**.**

1.1.3 Labeling Recommendations

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, INVOKAMET is not recommended during the second and third trimesters of pregnancy. Limited data with INVOKAMET or canagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *[see Data].* There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations].*

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered at an exposure 0.5-times the 300 mg clinical dose, based on AUC during a period of renal development corresponding to the late second and third trimesters of human pregnancy. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Canagliflozin

Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1 month recovery period. In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Metformin Hydrochloride

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- and 6-times a 2000 mg clinical dose based on body surface area (mg/m2) for rats and rabbits, respectively.

Canagliflozin and Metformin

No adverse developmental effects were observed when canagliflozin and metformin were coadministered to pregnant rats during the period of organogenesis at exposures up to 11 and 13 times, respectively, the 300 mg and 2000 mg clinical doses of canagliflozin and metformin based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKAMET or canagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk *[see Data]*. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKAMET is not recommended while breastfeeding.

Data

Human Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Animal Data

Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of INVOKAMET in pediatric patients under 18 years of age have not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b)(4)

No animal studies have been conducted with the combined products in INVOKAMET to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on findings in studies with canagliflozin and metformin individually.

Canagliflozin

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Sprague-Dawley rats. Canagliflozin did not increase the incidence of tumors in mice dosed at 10, 30, or 100 mg/kg (less than or equal to 14 times exposure from a 300 mg clinical dose).

Testicular Leydig cell tumors, considered secondary to increased luteinizing hormone (LH), increased significantly in male rats at all doses tested (10, 30, and 100 mg/kg). In a 12-week clinical study, LH did not increase in males treated with canagliflozin.

Renal tubular adenoma and carcinoma increased significantly in male and female rats dosed at 100 mg/kg, or approximately 12-times exposure from a 300 mg clinical dose. Also, adrenal pheochromocytoma increased significantly in males and numerically in females dosed at 100 mg/kg. Carbohydrate malabsorption associated with high doses of canagliflozin was considered a necessary proximal event in the emergence of renal and adrenal tumors in rats. Clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the recommended clinical dose of 300 mg.

Mutagenesis
Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was mutagenic in the *in vitro* mouse lymphoma assay with but not without metabolic activation. Canagliflozin was not mutagenic or clastogenic in an *in vivo* oral micronucleus assay in rats and an *in vivo* oral Comet assay in rats.

Metformin
Carcinogenesis
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis
There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility
Canagliflozin had no effects on the ability of rats to mate and sire or maintain a litter up to the high dose of 100 mg/kg (approximately 14 times and 18 times the 300 mg clinical dose in males and females, respectively), although there were minor alterations in a number of reproductive parameters (decreased sperm velocity, increased number of abnormal sperm, slightly fewer corpora lutea, fewer implantation sites, and smaller litter sizes) at the highest dosage administered.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

1.2 Brief Discussion of Nonclinical Findings

The sponsor is seeking the approval of canagliflozin as a fixed dose combination with metformin XR (INVOKAMET® XR). The extended release bilayer formulation tablets are designed to be two tablets taken once a day (strengths of 50/500, 50/1000, 150/500 and 150/1000 mg of canagliflozin/metformin XR). The sponsor has cross-referenced the canagliflozin NDA 204042 (INVOKANA®) and metformin NDA 21748 (GLUMETZA®) for safety and efficacy.
Canagliflozin is a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor approved by the FDA in March 29, 2013. As a selective SGLT2inhibitor, the antihyperglycemic effect of canagliflozin comes from its ability to reduce the renal threshold for glucose reabsorption, leading to spillage of glucose to the urine. This process is independent of insulin. Although canagliflozin is approximately 160 fold more selective to renal SGLT2 (IC_{50} 4.1 nM) than SGLT1 (IC_{50} 664 nM), at high concentrations, it is capable of inhibiting intestinal SGLT1 in rats.

Metformin XR is a biguanide class insulin sensitizer antihyperglycemic agent approved by the FDA on June 3, 2005. Metformin hydrochloride XR (JNJ-1158196) is a biguanide class drug that lowers both basal and postprandial glucose by decreasing hepatic glucose production and intestinal glucose absorption. Metformin also improves insulin sensitivity by increasing peripheral glucose uptake and utilization. There is extensive clinical experience with use of metformin in type 2 diabetic adults and pediatric population. Although both metformin IR and XR are available for adults, only metformin IR is available to children in US.

The INVOKAMET® XR tablets contain several inactive ingredients. However, all the excipients and (b)(4) materials have been well characterized, listed in the inactive ingredients data list. They are widely used in drug formulations approved by the FDA and considered safe. The safety of both canagliflozin and metformin has been reviewed under the referenced application. The potential interaction between the canagliflozin and metformin have been addressed with a 3-Month rat combination toxicology and a rat embryofetal development (EFD) study submitted to NDA 204042 (canagliflozin) and reviewed for NDA 204353 (canagliflozin + metformin IR combination). The addition of 300 mg/kg metformin to canagliflozin (Cana/Met doses: 4/300, 20/300 and 100/300 mg/kg/day), had no impact on the toxicological profile of canagliflozin in rats. Metformin had no impact on canagliflozin exposure; however, canagliflozin increased metformin AUC exposure by as much as 1.8 fold in rats. 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. In the EFD study, the addition of metformin did not alter the canagliflozin associated decrease in maternal body weight and fetal skeletal variations such as reduced or incomplete ossification. The transient variations in fetal skeletal ossification were also seen with metformin alone but at lower incidence and unlikely to be clinically meaningful.
In summary, the finding of safety for both canagliflozin and metformin are applicable to the extended release formulation. The inactive ingredients in the extended release formulation do not change the applicability of the toxicology studies conducted for each component and combination (canagliflozin + metformin). The nonclinical studies in the referenced NDAs support the safety and approval of the canagliflozin–metformin XR FDC tablets.

2 Drug Information

2.1 Drug: INVOKAMET®

2.1.2 Generic Name: Canagliflozin+metformin XR

2.1.3 Code Name for canaglifllozin: JNJ-28431754 hemihydrate

Code Name for metformin: JNJ-1158196-AAC (metformin hydrochloride)
Janssen is purchasing metformin from [redacted] (b)(4) A letter of authorization was provided by [redacted] (b)(4) to reference DMF [redacted] (b)(4)

2.1.4 Chemical Name

canagliflozin: (1S)-1,5-anhydro-1-C-[3-[[5-(4-fluorophenyl)-thienyl]methyl] -4-methylphenyl]-D-Glucitol

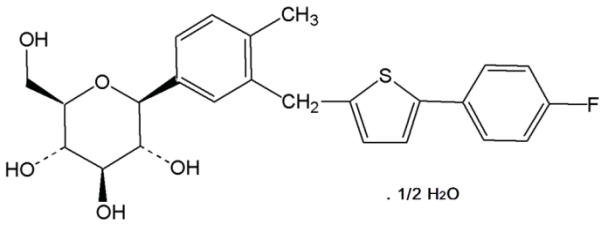
metformin: 1,1-Dimethylbiguanide hydrochloride, N,N-dimethyl-monochloride, imidodicarbonimidic diamide

2.1.5 Molecular Formula/Molecular Weight

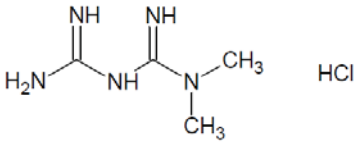
Canagliflozin hemihydrate: $C_{24}H_{25}FO_5S.\ H_2O$, MW 454.5

Me**tformin hydrochloride:** $C_4H_{11}N_5.\ HCl$, MW 165.6

2.1.6 Structure of canagliflozin (JNJ-28431754-ZAE):



Structure of metformin (JNJ-1158196-AAC):



2.1.7 Pharmacologic class:

Canagliflozin: Sodium glucose co-transporter 2 (SGLT2) inhibitor
Metformin: Biguanide antihyperglycemic

2.2 Relevant IND/s, NDA/s, and DMF/s

Canagliflozin NDA 204042 (IND 76479, (b)(4) 110533)
Metformin hydrochloride DMF (b)(4) is approved and marketed in US as Glumetza (NDA 21748).

2.3 Clinical Formulation

2.3.1 Drug Formulation

Active ingredients: JNJ-28431754 hemihydrate IR and Metformin hydrochloride XR
50/500 CANA/MET XR FDC tablets (b)(4)
50/1000 CANA/MET XR FDC tablets (pink)
150/500 CANA/MET XR FDC tablets (orange)
150/1000 CANA/MET XR FDC tablets (b)(4)

Inactive ingredients:

(b)(4)

2.3.3 Comments on Impurities/Degradants of Concern in canagliflozin

Canagliflozin Impurities
The total impurities in canagliflozin (JNJ-28431754) are no more than (b)(4)% with unspecific impurities less than (b)(4)%. Inorganic impurities such as (b)(4)

Metformin Impurities
The total impurities in metformin are no more than (b)(4)%. Individual impurities are less than the specification (b)(4)%), requiring no characterization. Inorganic impurities such as (b)(4)

2.4 Proposed Clinical Population and Dosing Regimen for canagliflozin +metformin

Type II diabetic patients, Canagliflozin-Metformin XR fixed dose combinations:
50/500, 50/1000, 150/500 and 150/1000 mg QD

2.5 Regulatory Background

The sponsor is seeking regulatory approval of NDA 205879, a once a orally administered fixed dose combination of canagliflozin/metformin XR. Pre-NDA meeting with the sponsor was held on June 25, 2014. The sponsor has cross-referenced the nonclinical data provide for the approval of canagliflozin under NDA 204042 (INVOKANA approved on March 29, 2013) and metformin HCl data under NDA 21748 (GLUMETZA approved on 3 June 2005). Canagliflozin FDC with metformin hydrochloride immediate release (IR) was approved on Aug 8, 2014 (NDA 205879. No new nonclinical studies were required nor submitted.

3.1 Studies Reviewed: None

3.3 Previous Reviews Referenced

The sponsor has cross-referenced the canagliflozin NDA 204042 (INVOKANA®) and metformin NDA 21748 (GLUMETZA®) for safety and efficacy. Acute and subchronic toxicology studies with canagliflozin alone and in combination with metformin (Study # TOX9521, Study # TOX959) have been reviewed attached to both NDA 204042 and NDA 204353. In the 3-month combination toxicology study in rats (Cana/Met doses: 4/300, 20/300 and 100/300 mg/kg/day), the addition of 300 mg/kg metformin had no impact on the toxicological profile of canagliflozin. In the EFD study, administration of canagliflozin with or without metformin was associated with dose-dependent decreases in maternal body weight and fetal skeletal variations such as reduced or incomplete ossification. The transient variations in fetal skeletal ossification were also seen with metformin alone but at lower incidence. Since these changes are transient, they are unlikely to be clinically meaningful. The XR formulation does not appreciably change daily exposure to either canagliflozin or to metformin; therefore, the prior toxicology studies with the combination are applicable to the current product. The nonclinical combination dose studies support the safety and approval of canagliflozin-metformin XR tablets.

Bioequivalence Studies:

The exposure to CANA/MET XR FDC formulation was compared to the individual components (canagliflozin + metformin XR) under various conditions in multiple bioequivalence studies in humans. The objectives of these studies were to show that the bioavailability, Cmax and AUC for the extended release FDC were similar to canagliflozin plus metformin XR (Glumetza). The doses and the conditions of the studies are shown in the tables below for both canagliflozin and metformin. These bioequivalence studies found both canagliflozin/metformin XR FDC to be similar to the reference components, indicating that the exposure provided by the XR formulation is sufficiently similar to the individual components to allow reliance on the nonclinical program for the extended release FDC formulation (INVOKAMET XR).

Canagliflozin exposure following oral administration of CANA/MET XR FDC formulation compared to reference (canagliflozin + metformin XR)

Canagliflozin (JNJ-28431754)/Metformin Hydrochloride (JNJ-1158196) Extended Release Fixed Dose Combination (CANA/MET XR FDC) Tablets
Pharmacokinetic Parameters of Canagliflozin

			Median (Range)	Arithmetic Mean (Standard Deviation)					
Dose (mg)	Formulation	N	t_{max} (h)	C_{max} (ng/mL)	$C_{min,ss}$ (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{∞} (ng.h/mL)	$t_{1/2}$ (h)	Study ID
100/1,000	CANA/MET XR FDC diluted CANA layer	18	3.00 (1.98-8.00)	726 (270)	NA	7,845 (1,724)	8,069 (1,739)	12.9 (5.14)	DIA1033
	Reference(Single Agent CANA + Glumetza)	18	3.00 (2.00-12.0)	697 (239)	NA	8,056 (1,589)	8,252 (1,620)	13.8 (4.05)	
100/1,000	Reference(Single Agent CANA + Glumetza)	41	3.00 (0.98 – 8.00)	965 (223)	NA	9,716 (2,300)[a]	9,935 (2,380)[b]	14.0 (4.12)[b]	DIA1041
	CANA/MET XR FDC Test 1 (JOLLC, Gurabo MET granulate)	41	3.00 (1.48 – 8.00)	959 (263)	NA	9,829 (2,279)	10,090 (2,386)	14.3 (3.37)	
	CANA/MET XR FDC Test 2 ((b)(4) (b)(4) MET granulate)	42	3.00 (1.00 – 12.0)	919 (234)	NA	9,743 (2,341)	10,000 (2,438)	13.7 (3.98)	
100/2,000	CANA/MET XR FDC diluted CANA layer	17	3.00 (1.98-12.0)	677 (155)	NA	7,356 (1,616)	7,541 (1,638)	12.7 (3.97)	DIA1033
	Reference(Single Agent CANA + Glumetza)	16	3.50 (2.00-8.00)	699 (124)	NA	7,482 (1,674)	7,655 (1,694)	12.2 (2.93)	
100/2,000	Reference (Single Agent CANA + Glumetza)	42	2.98 (0.50 – 6.03)	1,010 (261)	NA	10,361 (2,989)[c]	10,653 (3,116)[c]	14.0 (4.04)[c]	DIA1062
	CANA/MET XR FDC Test 1 (JOLLC, Gurabo MET granulate)	41	2.05 (0.98 – 6.05)	973 (344)	NA	9,899 (2,856)	10,201 (2,955)[a]	14.4 (4.09)[a]	
	CANA/MET XR FDC Test 2 ((b)(4) (b)(4) MET granulate)	40	3.00 (1.00 – 8.00)	1,010 (259)	NA	10,482 (2,812)	10,708 (2,928)[b]	13.0 (3.20)[b]	
150/1,000	CANA/MET XR FDC, Fasted	24	1.98 (0.98 – 4.00)	1,449 (362)	NA	12,203 (2,530)	12,487 (2,606)	13.9 (2.65)	DIA1064
	CANA/MET XR FDC, Fed	24	2.00 (1.00 – 6.00)	1,274 (278)	NA	12,659 (2,419)	13,001 (2,547)	14.0 (2.48)	
300/1,000	CANA/MET XR FDC undiluted CANA layer	18	4.00 (2.00-8.00)	2,278 (739)	NA	24,930 (5,550)	25,451 (5,790)	12.7 (2.64)	DIA1033
	Reference (Single Agent CANA + Glumetza)	18	4.00 (2.00-8.00)	2,127 (674)	NA	24,685 (5,323)	25,208 (5,552)	12.6 (2.91)	
	CANA/MET XR FDC diluted CANA layer	18	3.99 (1.00-8.00)	2,098 (589)	NA	24,059 (5,810)	24,621 (6,055)	13.3 (3.29)	

Metformin exposure following oral administration of CANA/MET XR FDC formulation compared to reference (canagliflozin + Metformin XR)

Canagliflozin (JNJ-28431754)/Metformin Hydrochloride (JNJ-1158196) Extended Release Fixed Dose Combination (CANA/MET XR FDC) Tablets
Pharmacokinetic Parameters of Metformin

			Median (Range)	Arithmetic Mean (Standard Deviation)					
Dose (mg)	Formulation	N	t_{max} (h)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{∞} (ng.h/mL)	$t_{1/2}$ (h)	Study ID
100/1,000	CANA/MET XR FDC diluted CANA layer	18	8.00 (5.98-10.0)	1,077 (271)	NA	11,596 (2,868)	12,129 (2,637)[a]	5.82 (1.94)[a]	DIA1033
	Reference (Single Agent CANA + Glumetza)	18	8.00 (6.00-10.0)	1,070 (305)	NA	11,867 (3,270)	12,461 (3,310)[b]	6.01 (2.19)[b]	
100/1,000	Reference (Single Agent CANA + Glumetza)	41	6.00 (4.00 – 12.0)	1,060 (221)	NA	11,645 (2,080)[c]	11,823 (2,131)[d]	5.55 (2.57)[d]	DIA1041
	CANA/MET XR FDC Test 1 (JOLLC, Gurabo MET granulate)	41	6.00 (4.00 – 10.0)	1,060 (216)	NA	11,478 (2,476)	11,643 (2,512)[c]	5.69 (2.87)[c]	
	CANA/MET XR FDC Te 2 (b)(4) MET granulate)	42	6.00 (4.00 – 10.0)	1,090 (228)	NA	11,893 (2,392)	12,038 (2,433)[e]	5.16 (1.79)[e]	
100/2,000	CANA/MET XR FDC diluted CANA layer	17	6.00 (4.00-8.00)	1,555 (373)	NA	17,966 (5,090)	18,593 (5,252)[b]	5.93 (2.68)[b]	DIA1033
	Reference (Single Agent CANA + Glumetza)	16	6.00 (4.00-8.00)	1,555 (302)	NA	18,851 (4,514)	19,271 (4,660)	6.08 (1.54)	
100/2,000	Reference (Single Agent CANA + Glumetza)	42	7.05 (3.98 – 12.0)	2,160 (447)	NA	26,150 (5,788)[e]	26,634 (5,875)[e]	5.56 (1.36)[e]	DIA1062
	CANA/MET XR FDC Test 1 (JOLLC, Gurabo MET granulate)	41	7.97 (4.00 – 12.0)	2,260 (542)	NA	26,787 (5,490)	27,344 (5,673)[d]	5.42 (1.01)[d]	
	CANA/MET XR FDC Te 2 (b)(4) MET granulate)	40	6.04 (4.00 – 10.0)	2,290 (559)	NA	26,369 (5,206)	26,988 (5,362)[f]	6.08 (2.75)[f]	
150/1,000	CANA/MET XR FDC, Fasted	24	4.00 (1.97 – 4.00)	874 (337)	NA	6,626 (2,539)	7,270 (2,623)[g]	10.9 (7.41)[g]	DIA1064
	CANA/MET XR FDC, F	24	6.00 (4.00 – 10.0)	940 (211)	NA	10,777 (1,946)	11,059 (1,940)[h]	5.45 (1.74)[h]	
300/1,000	CANA/MET XR FDC undiluted CANA layer	18	8.00 (6.00-8.00)	1,112 (237)	NA	12,306 (2,536)	12,573 (2,555)	6.92 (4.00)	DIA1033
	CANA/MET XR	18	8.00 (6.00-12.0)	1,027 (170)	NA	11,686 (2,457)	11,776 (2,452)[b]	6.05 (1.97)[b]	
	FDC diluted CANA layer	18	6.00 (4.00-10.0)	1,044 (206)	NA	11,815 (2,220)	12,095 (2,310)[a]	7.02 (4.03)[a]	
300/1,000	Reference (Single Agent CANA + Glumetza)	38	7.99 (4.00 – 10.0)	1,040 (232)	NA	11,569 (2,911)	11,739 (2,993)[i]	5.96 (2.57)[i]	DIA1063
	CANA/MET XR FDC Te 1 (JOLLC, Gurabo MET granulate)	37	8.00 (5.98 – 10.0)	1,050 (234)	NA	11,301 (2,274)	11,483 (2,322)	6.16 (3.01)	
	CANA/MET XR FDC Te 2 (b)(4) MET granulate)	39	6.00 (4.00 – 12.0)	1,050 (304)	NA	11,135 (3,298)	11,255 (3,359)[f]	5.83 (2.22)[f]	
300/2,000	CANA/MET XR FDC (Day 1)	12	10.0 (4.00 – 10.0)	1,434 (285)	NA	16,604 (3,282) [$AUC_{\tau,ss}$]	NA	NA	DIA1042
	CANA/MET XR FDC (Day 7)	10	8.00 (4.00 – 12.0)	1,581 (251)	183 (54.8)	NA	19,386 (3,454) [$AUC_{\tau,ss}$]	7.14 (0.730)	
300/2,000	CANA/MET XR FDC undiluted CANA layer	18	8.00 (4.00-10.0)	1,719 (314)	NA	19,216 (3,441)	19,980 (3,362)[a]	7.51 (3.93)[a]	DIA1033
	Reference (Single Agent CANA + Glumetza)	18	8.00 (4.00-12.0)	1,611 (320)	NA	19,506 (3,835)	19,987 (3,883)	6.73 (2.21)	
300/2,000	Reference (Single Agent CANA + Glumetza)	47	7.98 (4.00-12.00)	2,180 (587)	NA	25,323 (6,029)	25,747 (6,101)	5.68 (2.58)	DIA1044
	CANA/MET XR FDC Test 1 (JOLLC, Gurabo MET granulate)	41	6.02 (4.00-10.00)	2,230 (450)	NA	24,828 (5,267)	25,634 (5,244)[f]	6.30 (2.57)[f]	
	CANA/MET XR FDC Test 2 (b)(4) MET granulate)	44	6.00 (4.00 – 10.03)	2,280 (468)	NA	25,870 (6,116)	26,223 (6,200)[j]	6.54 (3.39)[j]	

[a] n=17; [b] n=16; [c] n=40; [d] n=39; [e] n=41; [f] n=38; [g] n=21; [h] n=23; [i] n=37; [j] n=43;
CANA=Canagliflozin; MET=Metformin; FDC=Fixed Dose Combination; NA=Not applicable: XR=Extended release
Note: Undiluted" means that the CANA granulation composition is identical to that of the single agent tablet being used as the reference in this study whereas "diluted" means that the granulation is more dilute [contains higher quantities of excipients] compared to the granulation of the single agent tablet.

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/s/

FRED K ALAVI
05/31/2016
Recommend approval of INVOKAMET XR

TODD M BOURCIER
05/31/2016