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RESEARCH**

APPLICATION NUMBER:

205879Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	205879 Serials 0000, 0008
Submission Date(s)	November 20, 2015 and May 23, 2016
Brand Name	INVOKAMET [®] XR
Generic Name	Canagliflozin (JNJ-28431754) /Metformin Hydrochloride Extended Release (JNJ-1158196)
Reviewer	Renu Singh, Ph.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Janssen Pharmaceuticals, Inc.
Formulation; Strength	Canagliflozin(mg)/Metformin (mg) Extended release tablets; 50/500, 150/500, 50/1000, and 150/1000
Relevant IND/NDA	IND 76,479; IND 110,533; NDA 204042; NDA 21748
Indication	An adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate

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1 Executive Summary

The applicant, Janssen Pharmaceuticals, Inc., has submitted NDA 205879 for INVOKAMET[®] XR, the fixed dose combination (FDC) of canagliflozin (CANA) and metformin (MET) extended-release (CANA/MET XR). Four dose strengths are proposed, including 50 mg/500 mg, 150 mg/500 mg, 50 mg/1000 mg, and 150 mg/1000 mg, intended to be taken as 2 tablets administered once daily (QD) with the morning meal. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with both canagliflozin and metformin is appropriate.

The NDA is submitted as a 505(b)(1) application and is based on the demonstration of bioequivalence (BE) of CANA/MET XR FDC to co-administration of canagliflozin and metformin hydrochloride (HCl) XR in healthy volunteers. The applicant is the sponsor of canagliflozin. Canagliflozin (100 mg and 300 mg film-coated tablets) was first approved for marketing in the US on 29 March 2013 under the tradename of INVOKANA[®] for the treatment of T2DM (NDA 204042). The sponsor provides a right-of-reference to the GLUMETZA[®] (metformin HCl XR tablets) NDA (21748) (approved on 03 June 2005).

In addition to the single agent, the applicant is the sponsor of CANA/MET immediate-release (IR) FDC, which was approved in the US (INVOKAMET[®]) (in dose strengths of 50 mg/500 mg, 50 mg/1000 mg, 150 mg/500 mg, and 150 mg/1000 mg) on 08 August 2014 (NDA 204353).

1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 205879 Clinical Pharmacology data submitted on November 20, 2015, and May 23, 2016 and recommends approval. Labeling recommendations are provided on page 19.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The applicant had submitted six pivotal biopharmaceutical studies conducted in healthy subjects to determine BE of CANA/MET XR FDC tablets compared to the individual components under fed conditions (standardized high fat meal), and to characterize the effects of food intake on the pharmacokinetics (PK) of canagliflozin and metformin after administration of the CANA/MET XR FDC tablet.

Pivotal BE studies: The to-be-marketed FDC tablet proposed by the applicant contains metformin HCl granulate manufactured at two sources (JOLLC, Gurabo referred as Treatment B and (b) (4) referred as Treatment C). CANA/MET XR FDC tablets made from both these sources were tested for BE. All BE studies were open-label, randomized, single-center, single-dose, 3-treatment, 3-period crossover studies conducted in healthy subjects under fed conditions (standardized high fat dinner).

CANA/MET XR FDC tablets were demonstrated to be bioequivalent with respect to equal doses of the individual components of canagliflozin and metformin HCl XR using the to-be-marketed CANA/MET XR FDC tablet strengths of 50 mg/500 mg, 150 mg/500 mg, 50 mg/1000 mg, and 150 mg/1000 mg (studies DIA1041, DIA1063, DIA1062, and DIA1044, respectively).

The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of C_{max} , AUC_{inf} , and AUC_{last} for canagliflozin and metformin after administration of XR FDC and individual tablets are shown in Table 1 (Treatment B) and 2 (Treatment C). The 90% CIs for the GMR of C_{max} , AUC_{inf} , and AUC_{last} were contained within the pre-specified BE limits of 80% to 125% for all comparisons. CANA/MET XR

FDC tablets with the 2 sources of metformin HCl granulate (Treatment B and C) were shown to be bioequivalent in these studies to the individual components. These BE results were confirmed by in-house analysis and found to be acceptable from clinical pharmacology perspective.

Table 1. 90% CI on the GMR of Canagliflozin and Metformin PK Parameters Following a Single Dose Oral Administration for Treatment B (JOLLC, Gurabo).

Study Description	Parameter	Canagliflozin GMR (90% CI)	Metformin GMR (90% CI)
DIA1041- CANA/MET XR FDC (2 x [50 mg/500 mg]) vs CANA (1 x 100 mg) + MET XR (2 x 500 mg)	C _{max} (ng/mL)	98.51 (91.46 – 106.10)	99.72 (95.03 – 104.63)
	AUC _{last} (ng h/mL)	100.94 (98.88 – 103.05)	97.15 (93.26 – 101.22)
	AUC _{inf} (ng.h/mL)	101.10 (99.05 – 103.19)	98.21 (94.28 – 102.29)
DIA1044 -CANA/MET XR FDC (2 x [150 mg/1000 mg]) vs CANA (1 x 300 mg) + MET XR (4 x 500 mg)	C _{max} (ng/mL)	92.25 (85.49 – 99.54)	106.04 (101.29 – 111.02)
	AUC _{last} (ng h/mL)	97.58 (95.74 – 99.46)	99.92 (96.08 – 103.91)
	AUC _{inf} (ng.h/mL)	97.57 (95.64 – 99.55)	102.45 (98.67 – 106.37)
DIA1062 - CANA/MET XR FDC (2 x [50 mg/1000 mg]) vs CANA (1 x 100 mg) + MET XR (4 x 500 mg)	C _{max} (ng/mL)	92.46 (86.10 – 99.28)	104.69 (99.55 – 110.09)
	AUC _{last} (ng h/mL)	93.60 (91.43 – 95.81)	102.43 (97.64 – 107.46)
	AUC _{inf} (ng.h/mL)	93.55 (91.25 – 95.91)	102.70 (97.61 – 108.05)
DIA1063 - CANA/MET XR FDC (2 x [150 mg/500 mg]) vs CANA (1 x 300 mg) + MET XR (2 x 500 mg)	C _{max} (ng/mL)	100.16 (92.41 – 108.57)	100.41 (94.86 – 106.28)
	AUC _{last} (ng h/mL)	98.75 (95.96 – 101.63)	98.84 (92.91 – 105.16)
	AUC _{inf} (ng.h/mL)	98.95 (96.05 – 101.93)	98.75 (92.53 – 105.40)

Source: Modified from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Pages 20-33.

Table 2. 90% CI on the GMR of Canagliflozin and Metformin PK Parameters Following a Single Dose Oral Administration for Treatment C (b) (4)

Study Description	Parameter	Canagliflozin GMR (90% CI)	Metformin GMR (90% CI)
DIA1041- CANA/MET XR FDC (2 x [50 mg/500 mg]) vs CANA (1 x 100 mg) + MET XR (2 x 500 mg)	C _{max} (ng/mL)	94.69 (87.91 – 101.99)	103.37 (98.52 – 108.47)
	AUC _{last} (ng.h/mL)	99.86 (97.82 – 101.94)	100.58 (96.54 – 104.78)
	AUC _{inf} (ng.h/mL)	99.96 (97.94 – 102.02)	99.93 (95.95 – 104.08)
DIA1044 -CANA/MET XR FDC (2 x [150 mg/1000 mg]) vs CANA (1 x 300 mg) + MET XR (4 x 500 mg)	C _{max} (ng/mL)	91.67 (84.96 – 98.91)	105.62 (100.89 – 110.56)
	AUC _{last} (ng.h/mL)	96.58 (94.76 – 98.43)	100.34 (96.49 – 104.34)
	AUC _{inf} (ng.h/mL)	96.57 (94.66 – 98.52)	101.72 (97.94 – 105.64)
DIA1062 - CANA/MET XR FDC (2 x [50 mg/1000 mg]) vs CANA (1 x 100 mg) + MET XR (4 x 500 mg)	C _{max} (ng/mL)	102.18 (95.15 – 109.73)	104.74 (99.59 – 110.15)
	AUC _{last} (ng.h/mL)	99.79 (97.48 – 102.15)	100.16 (95.47 – 105.08)
	AUC _{inf} (ng.h/mL)	99.41 (96.97 – 101.91)	100.57 (95.58 – 105.83)
DIA1063 - CANA/MET XR FDC (2 x [150 mg/500 mg]) vs CANA (1 x 300 mg) + MET XR (2 x 500 mg)	C _{max} (ng/mL)	103.46 (95.44 – 112.15)	98.95 (93.48 – 104.75)
	AUC _{last} (ng.h/mL)	97.87 (95.10 – 100.73)	95.63 (89.88 – 101.75)
	AUC _{inf} (ng.h/mL)	97.82 (94.95 – 100.77)	95.73 (89.68 – 102.20)

Source: Modified from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Pages 20-33.

Multiple-dose PK study: Study DIA1042 was conducted to assess the multiple-dose PK of canagliflozin and metformin XR following QD administration of 2 x 150/1000 mg CANA/MET XR FDC tablets in healthy subjects. This was an open-label, multiple-dose, single-center, PK study conducted in 12 healthy adult men and women for 7 days under fed conditions (standardized high fat meal).

The 150/1000 mg CANA/MET XR FDC tablet administered as 2 tablets at a total daily dose of 300 mg canagliflozin and 2000 mg metformin XR with a high fat dinner meal showed increases in canagliflozin of 33% and 36% for C_{max} and AUC_{tau} , respectively, and increases in metformin of 10% and 18% for C_{max} and AUC_{tau} , respectively, after 7 days of QD dosing relative to the C_{max} and AUC_{tau} following the first dose on Day 1. These accumulations in exposure parameters were expected based on the established PK of canagliflozin and metformin. Steady-state was attained by the 6th and 3rd doses for canagliflozin and metformin XR, respectively.

This study suggested that there was no evidence of dose dumping with CANA/MET XR FDC after multiple QD administration over 7 days.

Food effect study: Study DIA1064 was designed to evaluate the effect of high fat meal on the oral bioavailability of canagliflozin and metformin following administration of the 150/1000 mg CANA/MET XR FDC tablet. This was an open-label, randomized, single-center, and single-dose, 2-period crossover study conducted in 24 healthy subjects (16 men and 8 women).

Canagliflozin: In this study, mean canagliflozin plasma AUCs differed by less than 5% in the fed vs fasted state and mean C_{max} was approximately 12% lower under fed conditions. This change in mean C_{max} is not considered clinically meaningful. Median time to reach maximum concentration (t_{max}) of canagliflozin was approximately 2 hours following dose administration under fed and fasted conditions. Thus, food did not have a clinically meaningful effect on canagliflozin bioavailability and this result is consistent with previously conducted food effect studies for canagliflozin single-agent tablet.

Metformin: The median t_{max} for the metformin component of the CANA/MET XR FDC tablet was prolonged in the fed (6 hours) vs fasted state (4 hours), indicating a slower rate of absorption in the presence of food. Additionally, C_{max} was approximately 13% higher and AUC_{last} and AUC_{inf} were increased by approximately 72% and 61%, respectively in the presence of food. The XR technology used for the metformin XR component of the CANA/MET XR FDC tablet is the same as that used in GLUMETZA[®] 500 mg tablets. This magnitude of food effect on metformin exposures for the CANA/MET XR FDC tablet is consistent with that observed for GLUMETZA[®].

In summary, food did not have a clinically meaningful effect on canagliflozin exposure from the CANA/MET XR FDC tablet. Since the effect of food on metformin exposure from the CANA/MET XR FDC tablet was similar to that observed for GLUMETZA[®], and because GLUMETZA[®] is recommended to be administered with a meal to avoid gastrointestinal intolerance. Therefore, CANA/MET XR FDC tablets should be administered with a meal.

INVOKANA[®] is recommended to be administered with the first meal of the day whereas INVOKAMET[®] is recommended to be taken twice daily with meals. GLUMETZA[®] is recommended to be administered QD with the evening meal. While the BE studies were conducted with evening meals considering the recommendations for GLUMETZA[®], the sponsor was advised by the FDA (25 June 2014, Pre-NDA meeting for NDA 205879) that the CANA/MET XR FDC tablets should be dosed with the morning meal rather than the evening meal to avoid the potential for nighttime falls or accidents related to

nocturia and hypotension, particularly in susceptible patient populations at higher risk for volume depletion (i.e., age ≥ 75 years, eGFR < 60 mL/min/1.73 m², or on loop diuretics). This is consistent with the dosing for a recently approved SGLT2i/Metformin XR FDC, XIGDUO. Accordingly, CANA/MET XR FDC tablets should be administered with the morning meal.

Overall, Clinical Pharmacology data submitted for NDA 205879 is acceptable to support approval.

2. Question-Based Review

2.1. Background

Canagliflozin (INVOKANA[®]) is a member of a new drug class of sodium glucose co-transporter 2 (SGLT2) inhibitors. The low-affinity/high capacity SGLT2 transporter in the proximal renal tubule reabsorbs most of the filtered glucose. Pharmacologic inhibition of SGLT2 has been shown to decrease renal glucose reabsorption, and thereby increase urinary glucose excretion (UGE) and lower plasma glucose (PG).

Metformin HCl is an established oral antidiabetic drug in the biguanide class that is the first-line drug of choice for the treatment of T2DM, in patients without renal impairment. Metformin HCl XR is characterized in the GLUMETZA[®] prescribing information (NDA 21748, GLUMETZA[®] US Package Insert [USPI], 2011). The proposed indication for the CANA/MET XR FDC is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate.

INVOKANA[®] (NDA 204042) is indicated in the US as an adjunct to diet and exercise to improve glycemic control in adults aged 18 years and older with T2DM. INVOKAMET[®] (NDA 204353) is indicated 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. Metformin HCl extended release (500 mg and 1000 mg tablets) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM (NDA 21748).

In the NDA for canagliflozin (204042), the efficacy and safety of this agent added to ongoing treatment with metformin (alone or with another anti-hyperglycemic agent (AHA)) was extensively evaluated in Phase 2 (dose-range finding) and Phase 3 studies. The Phase 3 studies evaluated doses of 100 mg and 300 mg administered QD.

As agreed with the FDA at the pre-NDA meeting (25 June 2014), the applicant has provided the following information to bridge to results from the canagliflozin Phase 3 program (that examined QD dosing of 100 mg and 300 mg) to support the CANA/MET XR FDC tablet for the proposed indication:

- Four Phase 1 studies demonstrated the BE of the to-be-marketed CANA/MET XR FDC to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg (Studies DIA1041, DIA1063, DIA1062, and DIA1044, respectively). A relative bioavailability study (DIA1033) served as a pilot for the 4 Phase 1 BE studies.
- A Phase 1 food effect study (DIA1064) evaluated the effect of food on canagliflozin bioavailability following single-dose administration of the 150/1000 mg CANA/MET XR FDC tablet.

- A Phase 1 multiple-dose pharmacokinetic study (DIA1042) evaluated the multiple dose pharmacokinetics of 2 CANA/MET XR FDC tablets (150 mg/1000 mg each) followed by QD oral doses.
- DIA2001, a supportive Phase 2 add-on to metformin dose-range finding study, that confirmed the selection of the 100 mg and 300 mg daily doses of canagliflozin that were examined in the Phase 3 program.
- 6 Phase 3 studies which provide evidence for efficacy including 5 studies in subjects on a defined AHA background of either metformin alone (in 2 studies: DIA3006 and DIA3009) or metformin in combination with another AHA (in 3 studies: DIA3002, DIA3012, and DIA3015). The sixth add-on to metformin Phase 3 study offering primary support for the CANA/MET XR FDC is the insulin substudy of DIA3008 (CANagliflozin CardioVascular [CV] Assessment Study [CANVAS]). The DIA3008 insulin substudy examined the use of canagliflozin as add-on therapy in subjects on insulin alone or in combination with other oral AHAs, and had a pre-specified analysis of the efficacy and safety of the addition of canagliflozin to subjects on insulin and metformin.
- A seventh Phase 3 study (DIA3010) provided supportive data for the CANA/MET XR FDC; Study DIA3010 evaluated canagliflozin in older subjects (≥ 55 and ≤ 80 years) treated with T2DM on AHA therapy (diet and exercise alone or in combination with other AHAs including insulin).
- An additional pivotal Phase 3 study (DIA3011) was conducted to evaluate the efficacy, safety and tolerability of canagliflozin in combination with metformin as initial combination therapy in subject with T2DM.
- In addition, 2 datasets are included with this CANA/MET XR FDC NDA (DS1 and DS1-M) to support the safety and tolerability of the CANA/MET XR FDC through 26 weeks, as well as a summary of safety data through 31 December 2012 based on the Broad Dataset (also referred to as original DS3).

Clinical Pharmacology review focused on the result of 4 pivotal BE studies, 1 food effect study and 1 multiple-dose PK study.

The applicant proposed the following dosing for CANA/MET XR FDC in the NDA 205879 submission:

Individualize the starting dose of once-daily INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) based on the effectiveness and tolerability of the patient's current regimen:



- *In patients already treated with canagliflozin and metformin, switch to two INVOKAMET XR tablets containing the same daily dose of canagliflozin and the same, or nearest appropriate, daily dose of metformin.*

During the review it was noted that first bullet for the proposed dosing indicated (b) (4)
[REDACTED] The sponsor was sent the following information request on May 5 , 2016.

- “Confirm that in the proposed label, (b) (4)

The sponsor responded with a correction on May 10th, 2016 stating that the statement should read as follows:

- “In patients currently not treated with either canagliflozin or metformin, initiate therapy with two INVOKAMET XR tablets containing canagliflozin 50 mg and metformin 500 mg;”

2.1.1. What are the Clinical Pharmacology and Biopharmaceutics studies submitted in NDA 205879?

Seven clinical pharmacology studies (6 pivotal and 1 pilot) were submitted by the applicant (Table 3). One pilot bioavailability study, four pivotal BE studies under fed conditions (a high fat dinner) and one food effect study (high fat breakfast) with CANA/MET XR FDC tablets were conducted in healthy subjects. Additionally, a multiple-dose PK study (DIA1042) was conducted. This review focuses on the six pivotal studies.

Table 3. Overview of Clinical Studies Used to Characterize the Biopharmaceutical Properties of CANA/MET XR FDC

Study	Objective towards to-be-marketed CANA/MET XR FDC
DIA1041	BE for 50/500 XR FDC to the individual components of canagliflozin and metformin XR
DIA1062	BE for 50/1000 XR FDC to the individual components of canagliflozin and metformin XR
DIA1044	BE for 150/500 XR FDC to the individual components of canagliflozin and metformin XR
DIA1063	BE for 150/1000 XR FDC to the individual components of canagliflozin and metformin XR
DIA1042	7-day multiple QD PK study of the 150/1000 mg CANA/MET XR FDC
DIA1064	Food effect study following single-dose of 150/1000 mg CANA/MET XR FDC
DIA1033	Pilot BE Study

Source: Modified from Module 2.5. Clinical Summary, Page 17.

2.2. General Attributes

2.2.1. What is the composition of to-be-marketed formulation of CANA/MET FDC?

The CANA/MET XR FDC tablet formulations are designed as bilayer tablets: an IR layer containing canagliflozin (JNJ-28431754-ZAE) and an XR layer containing metformin HCl (JNJ-1158196-AAC). Appendix 4.1 shows the detailed composition of the to-be-marketed CANA/MET XR FDC tablets.

The canagliflozin IR layer was developed based on the marketed single component canagliflozin IR tablets (INVOKANA[®] 100 and 300 mg, NDA 204042). The same canagliflozin granulate is used for the CANA/MET XR FDC tablet formulations 150/500 mg (G042) and 150/1000 mg (G039). The 50/500 mg (G043) and 50/1000 mg (G045) formulations also contain this canagliflozin granulate, plus silicified microcrystalline cellulose (SMCC) (b) (4) The

metformin HCl XR layer is a polymer matrix which controls the drug release by passive diffusion through a swollen matrix in combination with tablet erosion.

The quantitative composition of the 500 mg metformin HCl XR layer in the CANA/MET XR FDC tablet formulations 150/500 mg (G042) and 50/500 mg (G043) (b) (4) to the commercial GLUMETZA[®] tablets 500 mg (NDA 021748) and contains polyethylene oxide (b) (4) and hypromellose (b) (4). The 1000 mg metformin HCl XR layer in the CANA/MET XR FDC tablet formulations 150/1000 mg (G039) and 50/1000 mg (G045) does (b) (4) polyethylene oxide (b) (4) and produces a dissolution profile similar to the formulations containing 500 mg metformin HCl.

Metformin HCl granulate for the CANA/MET XR FDC tablet were manufactured in 2 facilities 1) JOLLC, Gurabo (b) (4). Regardless of the metformin HCl granulate manufacturing site, the releasing-controlling polymers were added in JOLLC, Gurabo and compression of the bilayer tablets occurred in Gurabo. CANA/MET XR FDC tablets with metformin HCl granulate from both of these sources of were tested in the BE studies.

2.2.2. Were the to-be-marketed CANA/MET XR FDC tablets used for pivotal studies?

Tablets of the proposed commercial formulations (film-coated), manufactured at commercial scale, at the commercial site, and using final manufacturing equipment were used in the pivotal BE studies. However, few changes to the process optimization and synthesis were made after initiation of the pivotal BE studies.

Process optimization was performed to improve the physical characteristics of the 1000 mg granulate manufactured (b) (4). Drug product manufactured with the optimized 1000 mg metformin HCl granulation process (b) (4) and with the original granulation process (used for the pivotal BE studies) has been demonstrated to have comparable quality, similar metformin dissolution profiles, and similar stability behavior.

In late 2014, after completion of manufacturing of the CANA/MET XR FDC primary stability batches and after the completion of the pivotal BE studies, canagliflozin monohydrate was observed at the commercial crude synthesis step at the Janssen research laboratories located in Beerse, Belgium. Investigation of this issue triggered a change in the synthesis process of the canagliflozin drug substance, as to ensure consistent synthesis of the monohydrate at the crude step, and the hemihydrate in the final step. This new synthesis method will be used for commercial production.

One commercial scale batch of CANA/MET XR FDC tablets per strength was manufactured with canagliflozin synthesized with the new process, and put on accelerated and long-term stability. Batch results of these batches, presented in the Batch Analyses Section, demonstrate that tablets prepared with canagliflozin synthesized with the new synthesis process, have a quality profile similar to the primary stability / pivotal BE batches. One month of stability data of these batches show no marked differences in the stability behavior of tablet batches prepared with canagliflozin synthesized with the new synthesis process, compared to the primary stability / pivotal BE batches. For further details on this aspect of the application, readers are referred to CMC review.

2.2.3. What are the findings from OSIS inspection?

Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and analytical sites for one of the pivotal BE study DIA1044 (the other pivotal studies used the same bioanalytical and clinical site).

OSIS recommended accepting data without an on-site inspection because the listed sites were recently inspected by OSIS (see review by Shila S Nkah dated 03/08/2016 in DARRTS).

2.3. General Clinical Pharmacology

2.3.1. Are the single-dose exposures of CANA/MET FDC comparable to the individual components?

The objective of the 4 pivotal BE studies summarized in this section was to assess the BE of the proposed commercial formulations of the CANA/MET XR FDC tablets compared to equal doses of the individual components of canagliflozin (INVOKANA[®]) and metformin HCl XR (GLUMETZA[®]). Additionally, another objective was to demonstrate that CANA/MET XR FDC tablets using metformin HCl granulate manufactured at JOLLC, Gurabo (b) (4) were each bioequivalent to the reference products.

These 4 studies used the same study design but varied the FDC tablet studied, i.e., each study investigated 1 of the 4 proposed commercial dose strengths of the FDC tablets. The 4 BE studies were open-label, randomized, single-center, single-dose, 3-treatment, 3-period crossover studies conducted in healthy subjects under fed conditions (standardized high fat dinner). The 3 treatment arms are described below:

- Reference Arm: Concomitantly administered single agents canagliflozin (INVOKANA[®]) and metformin HCl XR (GLUMETZA[®]) 500 mg tablets.
- Test 1: CANA/MET XR FDC tablets using metformin HCl granulate manufactured in JOLLC, Gurabo (Treatment B).
- Test 2: CANA/MET XR FDC tablets using metformin HCl granulate manufactured (b) (4) (Treatment C).

The BE studies were conducted under fed conditions because metformin HCl XR is recommended to be taken with a meal to reduce the incidence of gastrointestinal side effects. The study design for pivotal BE studies is shown in Table 4.

Table 4. Study Design for Pivotal BE Studies

Study Sequence	Period 1	Period 2	Period 3
ABC (n=7)	Treatment A (Reference) CANA (1 x 100 mg) + MET XR (4 x 500 mg)	Treatment B (Test 1)* CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment C (Test 2)** CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])
ACB (n=7)	Treatment A (Reference) CANA (1 x 100 mg) + MET XR (4 x 500 mg)	Treatment C (Test 2) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment B (Test 1) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])
BAC (n=7)	Treatment B (Test 1) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment A (Reference) CANA (1 x 100 mg) + MET XR (4 x 500 mg)	Treatment C (Test 2) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])
BCA (n=7)	Treatment B (Test 1) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment C (Test 2) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment A (Reference) CANA (1 x 100 mg) + MET XR (4 x 500 mg)
CAB (n=7)	Treatment C (Test 2) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment A (Reference) CANA (1 x 100 mg) + MET XR (4 x 500 mg)	Treatment B (Test 1) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])
CBA (n=7)	Treatment C (Test 2) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment B (Test 1) CANA/MET XR FDC tablet (2 x [50 mg/1,000 mg])	Treatment A (Reference) CANA (1 x 100 mg) + MET XR (4 x 500 mg)

*Treatment B, Test 1: Gurabo-manufactured metformin HCl granulate and addition of release-controlling polymers to obtain the XR granulation/Gurabo-manufactured canagliflozin/Gurabo FDC tablet.

** Treatment C, Test 2: (b) (4) manufactured metformin HCl granulate/Gurabo-addition of release-controlling polymers to the metformin HCl granulate (b) (4) to obtain the XR granulation/Gurabo-manufactured canagliflozin/Gurabo FDC tablet.

Source: Module 5.3.1.2 Protocol 28431754DIA1062, Page 28.

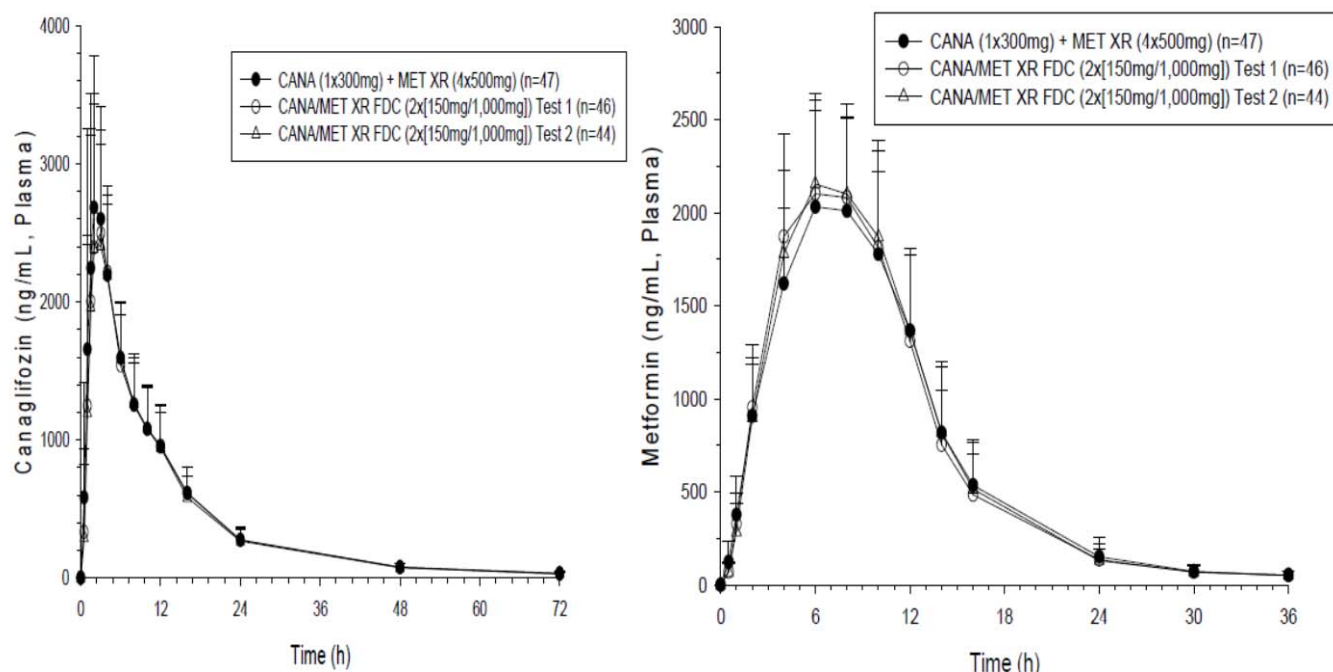
The mean plasma concentration-time profiles of canagliflozin and metformin were similar after administration of the FDC tablets and co-administration of the individual tablets. An example of the mean concentration-time profiles for canagliflozin and metformin components of the 150/1000 mg CANA/MET XR FDC tablet (JOLLC, Gurabo manufactured metformin HCl granulate) (Treatment B-Test 1) and the 150/1000 mg CANA/MET XR FDC tablet (b) (4) manufactured metformin HCl granulate), (Treatment C -Test 2) when administered as 2 tablets under fed conditions versus the individual components are shown in Figure 1.

The applicant's PK analysis dataset excluded subjects/data based on the following criteria that were pre-specified in the protocol:

- If the terminal phase could not be adequately characterized (i.e., $r^2_{adj} < 0.9$ or AUC_{inf} extrapolation $> 20\%$), terminal phase dependent PK parameters ($t_{1/2}$ and/or AUC) of CANA or MET XR were excluded from the descriptive statistics; AUC_{inf} values for these subjects were also excluded from the statistical analysis.
- Only the data from subjects who have evaluable pharmacokinetics for all 3 treatment periods was included in the statistical analysis of that particular pharmacokinetic parameter.
- If a subject vomits within 24 hours of dosing, the subject's data was excluded from the statistical analysis.

The geometric means (GMs), GMRs and 90% CIs for the 4 pivotal BE studies are presented in Table 5, 6, 7 and 8. The canagliflozin and metformin components of the CANA/MET XR FDC tablets (both treatment B and C) when administered as 2 tablets under fed conditions, met the predefined BE criteria for AUC_{inf} , AUC_{last} , and C_{max} relative to individual canagliflozin + metformin HCl XR as the 90% CIs for the test to reference GMRs of these parameters were entirely contained within the pre-specified BE limits of 80% to 125%.

Figure 1. Arithmetic Mean (SD) Plasma Concentration-Time Profiles of Canagliflozin (Left) and Metformin (Right) Following Administration of 2 × 150/1000 mg CANA/MET XR FDC Tablets and Equal Doses of the Individual Components (1 × 300 mg Canagliflozin and 4 × 500 Extended-Release Metformin HCl) Tablets (Study DIA1044)



Test 1: CANA/MET XR FDC (2 x [150/1000 mg]) (Treatment B, JOLLC, Gurabo manufactured metformin HCl granulate)
 Test 2: CANA/MET XR FDC (2 x [150/1000 mg]) (Treatment C, ^{(b) (4)} manufactured metformin HCl granulate)
 Source: Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Page 31.

Table 5. GMs and the GMRs with Corresponding 90% CIs for Canagliflozin Pharmacokinetic Parameters (Treatment B vs. Treatment A)

Study	Parameter	N	(Treatment B, Test 1)	(Treatment A, Reference)	Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
DIA1041			CANA/MET XR FDC (2 x [50 mg/500 mg])	CANA (1 x 100 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	41	924.84	938.84	98.51 (91.46 – 106.10)	20
	AUC _{last} (ng h/mL)	40	9,490.94	9,402.40	100.94 (98.88 – 103.05)	6
	AUC _{inf} (ng.h/mL)	39	9,707.13	9,601.75	101.10 (99.05 – 103.19)	5
DIA1044			CANA/MET XR FDC (2 x [150 mg/1000 mg])	CANA (1 x 300 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	39	2855.66	3095.73	92.25 (85.49 – 99.54)	20
	AUC _{last} (ng h/mL)	39	29439.20	30168.27	97.58 (95.74 – 99.46)	5
	AUC _{inf} (ng.h/mL)	37	30622.31	31383.57	97.57 (95.64 – 99.55)	5
DIA1062			CANA/MET XR FDC (2 x [50 mg/1,000 mg])	CANA (1 x 100 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	38	889.55	962.11	92.46 (86.10 – 99.28)	6
	AUC _{last} (ng h/mL)	38	9,367.97	10,008.70	93.60 (91.43 – 95.81)	6
	AUC _{inf} (ng.h/mL)	36	9652.16	10317.39	93.55 (91.25 – 95.91)	19
DIA1063			CANA/MET XR FDC (2 x [150 mg/500 mg])	CANA (1 x 300 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	36	2,949.05	2,944.25	100.16 (92.41 – 108.57)	21
	AUC _{last} (ng h/mL)	36	31,191.79	31,585.12	98.75 (95.96 – 101.63)	7
	AUC _{inf} (ng.h/mL)	35	31,995.65	32,336.63	98.95 (96.05 – 101.93)	7

Source: Modified from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Pages 20-33.

Table 6. GMs and the GMRs with Corresponding 90% CIs for Metformin Pharmacokinetic Parameters (Treatment B vs. Treatment A)

Study	Parameter	N	(Treatment B, Test 1)	(Treatment A, Reference)	Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
DIA1041			CANA/MET XR FDC (2 x [50 mg/500 mg])	CANA (1 x 100 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	41	1,035.23	1,038.15	99.72 (95.03 – 104.63)	13
	AUC _{last} (ng.h/mL)	40	11,083.21	11,407.87	97.15 (93.26 – 101.22)	11
	AUC _{inf} (ng h/mL)	37	11,286.97	11,492.95	98.21 (94.28 – 102.29)□	10
DIA1044			CANA/MET XR FDC (2 x [150 mg/1000 mg])	CANA (1 x 300 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	36	2203.80	2078.27	106.04 (101.29 – 111.02)	12
	AUC _{last} (ng.h/mL)	36	24135.29	24155.57	99.92 (96.08 – 103.91)	10
	AUC _{inf} (ng h/mL)	32	24843.07	24249.95	102.45 (98.67 – 106.37)	9
DIA1062			CANA/MET XR FDC (2 x [50 mg/1,000 mg])	CANA (1 x 100 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	38	2203.55	2104.86	104.69 (99.55 – 110.09)	13
	AUC _{last} (ng.h/mL)	38	26,102.76	25,483.73	102.43 (97.64 – 107.46)	13
	AUC _{inf} (ng h/mL)	36	26,539.77	25,841.88	102.70 (97.61 – 108.05)	13
DIA1063			CANA/MET XR FDC (2 x [150 mg/500 mg])	CANA (1 x 300 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	36	1,032.72	1,028.52	100.41 (94.86 – 106.28)	15
	AUC _{last} (ng.h/mL)	36	11,186.15	11,317.00	98.84 (92.91 – 105.16)	16
	AUC _{inf} (ng h/mL)	34	11,186.32	11,327.38	98.75 (92.53 – 105.40)	16

Source: Modified from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Pages 20-33.

Table 7. GMs and the GMRs with Corresponding 90% CIs for Canagliflozin Pharmacokinetic Parameters (Treatment C vs. Treatment A)

Study	Parameter	N	(Treatment C, Test 2)	(Treatment A, Reference)	Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
DIA1041			CANA/MET XR FDC (2 x [50 mg/500 mg])	CANA (1 x 100 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	41	889.00	938.84	94.69 (87.91 – 101.99)	20
	AUC _{last} (ng h/mL)	40	9,389.28	9,402.40	99.86 (97.82 – 101.94)	6
	AUC _{inf} (ng.h/mL)	39	9,597.93	9,601.75	99.96 (97.94 – 102.02)	5
DIA1044			CANA/MET XR FDC (2 x [150 mg/1000 mg])	CANA (1 x 300 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	39	2837.95	3095.73	91.67 (84.96 – 98.91)	20
	AUC _{last} (ng h/mL)	39	29136.75	30168.27	96.58 (94.76 – 98.43)	5
	AUC _{inf} (ng.h/mL)	37	30306.38	31383.57	96.57 (94.66 – 98.52)	5
DIA1062			CANA/MET XR FDC (2 x [50 mg/1,000 mg])	CANA (1 x 100 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	38	983.12	962.11	102.18 (95.15 – 109.73)	19
	AUC _{last} (ng h/mL)	38	9,987.69	10,008.70	99.79 (97.48 – 102.15)	6
	AUC _{inf} (ng.h/mL)	36	10,256.01	10,317.39	99.41 (96.97 – 101.91)	6
DIA1063			CANA/MET XR FDC (2 x [150 mg/500 mg])	CANA (1 x 300 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	36	3,046.04	2,944.25	103.46 (95.44 – 112.15)	21
	AUC _{last} (ng h/mL)	36	30,913.42	31,585.12	97.87 (95.10 – 100.73)	7
	AUC _{inf} (ng.h/mL)	35	31,631.85	32,336.63	97.82 (94.95 – 100.77)	7

Source: Modified from Module 2.7.1, Summary of Biopharmaceutical Studies and Associated Analytical Methods, Pages 20-33.

Table 8. GMs and the GMRs with Corresponding 90% CIs for Metformin Pharmacokinetic Parameters (Treatment C vs. Treatment A)

Study	Parameter	N	(Treatment C, Test 2)	(Treatment A, Reference)	Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
DIA1041			CANA/MET XR FDC (2 x [50 mg/500 mg])	CANA (1 x 100 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	41	1,073.17	1,038.15	103.37 (98.52 – 108.47)	13
	AUC _{last} (ng h/mL)	40	11,473.72	11,407.87	100.58 (96.54 – 104.78)	11
	AUC _{inf} (ng.h/mL)	37	11,484.90	11,492.95	99.93 (95.95 – 104.08)	10
DIA1044			CANA/MET XR FDC (2 x [150 mg/1000 mg])	CANA (1 x 300 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	36	2194.97	2078.27	105.62 (100.89 – 110.56)	12
	AUC _{last} (ng h/mL)	36	24236.89	24155.57	100.34 (96.49 – 104.34)	10
	AUC _{inf} (ng.h/mL)	32	24666.84	24249.95	101.72 (97.94 – 105.64)	9
DIA1062			CANA/MET XR FDC (2 x [50 mg/1,000 mg])	CANA (1 x 100 mg) + MET XR (4 x 500 mg)		
	C _{max} (ng/mL)	38	2,204.62	2,104.86	104.74 (99.59 – 110.15)	13
	AUC _{last} (ng h/mL)	38	25,523.66	25,483.73	100.16 (95.47 – 105.08)	13
	AUC _{inf} (ng.h/mL)	36	25,990.22	25,841.88	100.57 (95.58 – 105.83)	13
DIA1063			CANA/MET XR FDC (2 x [150 mg/500 mg])	CANA (1 x 300 mg) + MET XR (2 x 500 mg)		
	C _{max} (ng/mL)	36	1,017.73	1,028.52	98.95 (93.48 – 104.75)	15
	AUC _{last} (ng h/mL)	36	10,822.75	11,317.00	95.63 (89.88 – 101.75)	16
	AUC _{inf} (ng.h/mL)	34	10,844.13	11,327.38	95.73 (89.68 – 102.20)	16

Source: Modified from Module 2.7.1, Summary of Biopharmaceutical Studies and Associated Analytical Methods, Pages 20-33.

2.3.2. Is there evidence of dose dumping with CANA/MET XR FDC?

As requested by the FDA during End of Phase 2 meeting (30 September 2010), the risk of alcohol-induced dose dumping for the modified release layer (metformin HCl) was evaluated by the applicant. They conducted in-vitro dissolution testing as well as multiple dosing PK to assess the potential for dose dumping.

An in-vitro alcohol interaction study was conducted to assess the potential for dose dumping with the CANA/MET XR FDC tablets at alcohol concentrations of 0%, 5%, 10%, 20%, and 40% (v/v). The study showed a decrease in in-vitro dissolution rate of metformin in the presence of 40% alcohol. The applicant reasoned that this decrease is caused by the limited solubility of metformin HCl in alcohol and the decreased solubility of polyethylene oxide in alcohol, resulting in a delay in the hydration of the polymer matrix. The applicant further added that, it is highly unlikely that alcohol concentrations of 40% will be maintained in the gastrointestinal tract for more than an hour after ingestion of alcohol, and even if there was a slight reduction in metformin exposure for a one-time event, this would not be expected to impact the overall efficacy profile of CANA/MET XR FDC.

To further confirm the lack of dose dumping potential for CANA/MET XR FDC the applicant conducted a multiple-dose PK Study DIA1042 of canagliflozin and metformin XR following QD administration of 2 x 150/1000 mg CANA/MET XR FDC tablets in healthy subjects. This was an open-label, multiple-dose, single-center, PK study conducted in 12 healthy adult men and women for 7 days under fed conditions (standardized high fat dinner meal).

This study showed that canagliflozin was absorbed quickly from the CANA/MET XR FDC tablets and achieved steady-state by the 6th dose (Figure 2). Median t_{max} was 2.5 hours (1.5 – 8 hours) and 1.75 hours (1.5 - 4 hours) on Days 1 and 7, respectively (Table 9). There was 36% accumulation in plasma based on AUC_{tau} after 7 days of QD dosing. The accumulation noted was expected based on the mean $t_{1/2}$ of 17.6 hours for canagliflozin. The canagliflozin PK results in this study are consistent with previously conducted studies (NDA 204042, module 2.7.2).

Metformin was absorbed at a much slower rate due to the extended release technology incorporated for metformin in the CANA/MET XR FDC tablets and achieved steady-state by the 3rd dose (Figure 2). Median t_{max} was 10 hours (4 – 10 hours) and 8 hours (4 – 12 hours) on Days 1 and 7, respectively (Table 10). The observed mean $t_{1/2}$ of 7.14 hours at steady-state is similar to the half-life after single-dose administration (approximately 5 to 7 hours) of the CANA/MET XR FDC tablets in the biopharmaceutics studies. There was 18% accumulation in plasma based on AUC_{tau} after 7 days of QD dosing. The accumulation noted was expected based on the mean $t_{1/2}$ observed for metformin. Metformin PK from the CANA/MET XR FDC tablets are consistent with previously reported metformin XR studies (NDA 21748).

Overall, these data suggest that the CANA/MET XR FDC tablets performed as expected and showed no evidence of dose dumping when administered with food in the repeated dose PK study.

Table 9. Arithmetic Mean (SD) Plasma Canagliflozin Pharmacokinetic Parameters

Parameter	Day 1 (N=12)	Day 7 (N=10a)
C _{max} (ng/mL)	2,318 (565)	3,078 (464)
C _{min,ss} (ng/mL)	NA	416 (109)
t _{max} (h) ^a	2.50 (1.50 – 8.00)	1.75 (1.50 – 4.00)
AUC _{tau,sd} (ng.h/mL)	19,505 (2,598)	NA
AUC _{tau,ss} (ng.h/mL)	NA	26,320 (3,672)
t _{1/2} (h)	NA	17.6 (5.52)
Accumulation Ratio ^b	NA	1.36 (0.143)

^aMedian (range); ^b Based on AUC

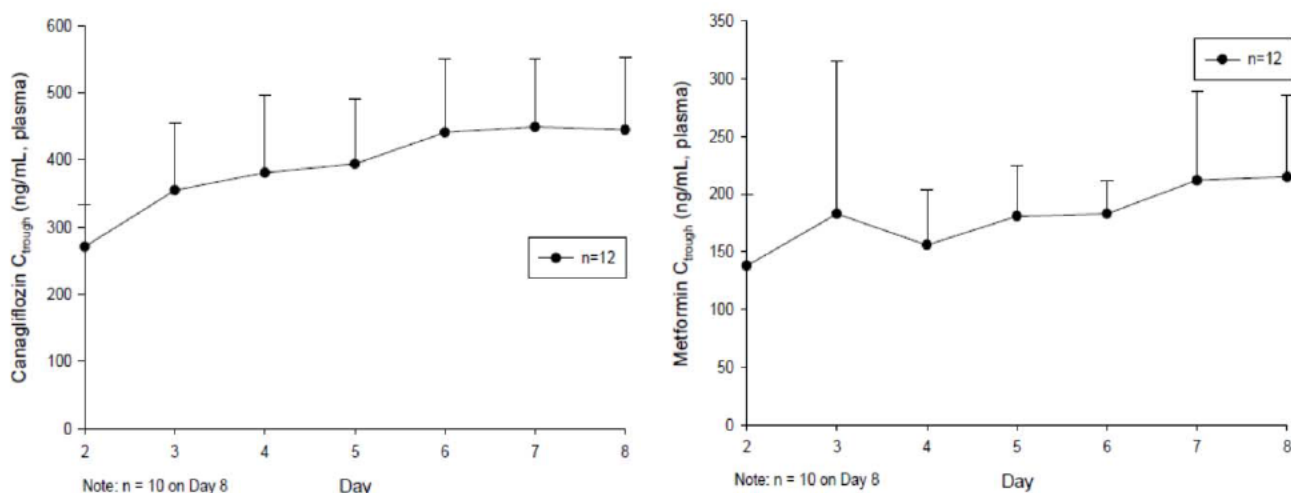
Source: Modified from Module 5.3.3.1 Study Report 28431754DIA1042, Page 29.

Table 10. Arithmetic Mean (SD) Plasma Metformin Pharmacokinetic Parameters

Parameter	Day 1 (N=12)	Day 7 (N=10a)
C _{max} (ng/mL)	1,434 (285)	1,581 (251)
C _{min,ss} (ng/mL)	NA	183 (54.8)
t _{max} (h) ^a	10.0 (4.00 – 10.0)	8.00 (4.00 – 12.0)
AUC _{tau,sd} (ng.h/mL)	16,604 (3,282)	NA
AUC _{tau,ss} (ng.h/mL)	NA	19,386 (3,454)
t _{1/2} (h)	NA	7.14 (0.730)
Accumulation Ratio ^b	NA	1.18 (0.231)

^aMedian (range); ^b Based on AUC

Source: Modified from Module 5.3.3.1 Study Report 28431754DIA1042, Page 31.

Figure 2. Arithmetic Mean (SD) Plasma Canagliflozin (Left) and Metformin (Right) C_{trough} Versus Time

Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Page 7.

2.3.3. How does food affect the bioavailability of CANA/MET XR FDC?

Study DIA1064 was designed to assess the effect of a high fat meal on the oral bioavailability of canagliflozin and metformin following administration of the 150/1000 mg CANA/MET XR FDC tablet, the highest dose strength of the proposed commercial XR FDC tablets, in healthy subjects.

This was an open-label, randomized, single-center, and single-dose, 2-period crossover study conducted in 24 healthy subjects (16 men and 8 women). In Period 1, subjects received one 150/1000 mg CANA/MET XR FDC tablet under either fasted (reference) or fed (test) conditions. Subjects received the alternate treatment during Period 2. For the fed treatment, study drug was administered 30 minutes after the start of a standardized, high fat breakfast in accordance with the agency’s guidance document on food effect studies.

The mean plasma concentration-time profiles of canagliflozin and metformin after single-dose administration of 1 x 150/1000 mg CANA/MET XR FDC tablet under fed and fasting conditions are shown in Figure 3.

The GMR and associated 90% CIs for C_{max} , AUC_{inf} , and AUC_{last} for canagliflozin and metformin after administration of the FDC tablet under fed conditions relative to fasted conditions are shown in Table 11. Food did not significantly affect canagliflozin t_{max} or AUC following single-dose administration of the 150/1000 mg CANA/MET XR FDC tablet but did lower mean C_{max} by approximately 12%. Metformin median t_{max} was prolonged in the fed (6 hours) vs fasted state (4 hours). Additionally, mean C_{max} was approximately 13% higher and mean AUC_{last} and AUC_{inf} were increased by approximately 72% and 61%, respectively in the presence of food. This magnitude of food effect on metformin exposures for the CANA/MET XR FDC tablet is consistent with that observed for GLUMETZA[®]. Based on these results CANA/MET XR FDC is recommended to be taken QD with morning meal.

Table 11. GMR and their Associated 90% CIs for Canagliflozin and Metformin Pharmacokinetic Parameters Following Administration of 1 x 150/1000 mg CANA/MET XR FDC Tablet With and Without Food

Parameter	Geometric Mean		Geometric Mean Ratio % (90% CI)
	Fed (N=24)	Fasted (N=24)	
Canagliflozin			
C_{max} (ng/mL)	1,241.78	1,408.34	88.17 (79.53; 97.75)
AUC_{last} (ng.h/mL)	12,455.18	11,956.54	104.17 (100.81; 107.64)
AUC_{inf} (ng.h/mL)	12,782.49	12,232.88	104.49 (101.20; 107.89)
Metformin			
C_{max} (ng/mL)	917.15	811.45	113.03 (98.64; 129.51)
AUC_{last} (ng.h/mL)	10,607.86	6,181.44	171.61 (152.83; 192.70)
AUC_{inf} (ng.h/mL) ^a	10,927.94	6,804.15	160.61 (143.20; 180.13)

^a n=20

N = maximum number of subjects with data.

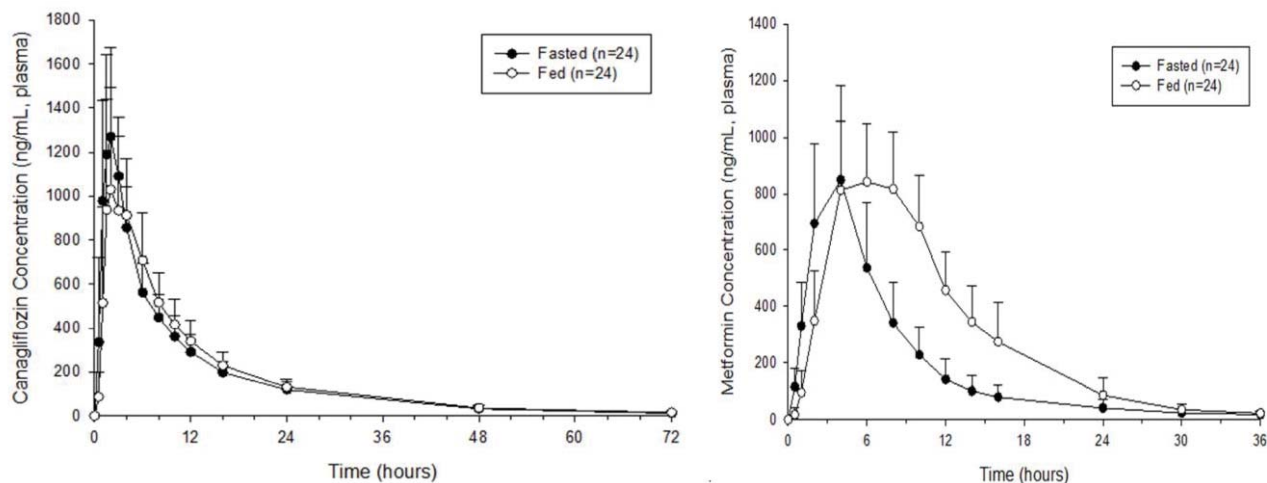
Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithm

Ref = Treatment A (CANA/MET XR FDC tablet, 1 x 150/1,000 mg) administered under fasted conditions

Test = Treatment B (CANA/MET XR FDC tablet, 1 x 150/1,000 mg) administered under fed conditions

Source: Modified from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Pages 36.

Figure 3. Arithmetic Mean (SD) Plasma Concentration-Time Profiles of Canagliflozin (Left) and Metformin (Right) Following Administration of 1 x 150/1000 mg CANA/MET XR FDC With and Without Food (Study DIA1064)



Source: Modified from Module 2.7.1, Summary of Biopharmaceutical Studies and Associated Analytical Methods, Pages 35.

2.4. Bioanalytical

2.4.1. Are the bioanalytical methods properly validated to measure canagliflozin and metformin in plasma samples?

The assays for analysis of canagliflozin and metformin in plasma were based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). The assay was validated according to the US FDA guidance (US FDA Bioanalytical Method Validation, 2001) and all acceptance criteria as specified in those guidelines were met (Appendix 4.2). All plasma PK samples from clinical studies with CANA/MET XR FDC were analyzed using this validated method.

Validated concentration range for canagliflozin was 5.0 ng/mL to 5000 ng/mL in plasma and 5.0 to 2500 ng/mL for metformin. The bioanalytical assay for pivotal studies showed acceptable inter-run precision and inter-run bias (Table 12). No notable SOP deviation was noted in the bioanalysis for the pivotal studies. A review of the bioanalysis showed that the validation and study assays were acceptable and adequately supported the BE studies.

Table 12. Summary of Bioanalytical Assay for Pivotal Biopharmaceutical Studies

Study	Drug	LLQ (ng/mL)	Inter-run precision (% CV)	Inter-run bias (%)
DIA 1041	Canagliflozin	5	≤3.7	-0.7 to 3.9
	Metformin	5	≤3.1	-3.6 to 2.4
DIA 1062	Canagliflozin	5	≤3.1	-3 to 5.9
	Metformin	5	≤9.5	-5.9 to 4.7
DIA 1044	Canagliflozin	5	≤6.3	0 to 6.0
	Metformin	5	≤5.8	0 to 3.5
DIA 1063	Canagliflozin	5	≤7.2	-5.7 to 3
	Metformin	5	≤3.5	-5.8 to 3.4
DIA 1042	Canagliflozin	5	≤4.3	-2.5 to 3.5
	Metformin	5	≤6.4	-7.6 to 6.4
DIA 1064	Canagliflozin	5	≤4	-3.5 to 4
	Metformin	5	≤3.1	-7.7 to 5.6

Source: Reviewer's summary of bioanalytical data in Module 5.3.1 and 5.3.3.

3. Label Recommendations

Red strikethrough text means deletion of the sponsor's proposed text. Blue underscored text means recommended addition.

12.3 Pharmacokinetics

INVOKAMET XR

(b) (4)

Absorption

Canagliflozin

The mean absolute oral bioavailability of canagliflozin is approximately 65%.

Metformin

Following a single oral dose of 1,000 mg (two 500 mg tablets) metformin extended-release after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7-8 hours. In both single and multiple-dose studies in healthy subjects, once daily 1,000 mg (two 500 mg tablets) dosing (b) (4) results in (b) (4) up to 35% higher C_{max} , of metformin relative to the immediate-release given as 500 mg twice daily without any change in overall systemic exposure, as measured by AUC.

4. Appendix

4.1. Formulation composition of CANA/MET XR FDC tablets.

Table 2: Formulation Composition Statement of the Cana/Met XR FDC Tablets

Component	Quality Reference ^a	Function	50/500 mg (G043)		50/1000 mg (G045)		150/500 mg (G042)		150/1000 mg (G039)	
			%w/w	mg/unit	%w/w	mg/unit	%w/w	mg/unit	%w/w	mg/unit
<i>Canagliflozin IR Layer</i>										
<i>Canagliflozin granulate</i>										
Canagliflozin	Company Specification	Active	(b) (4)	51.00 ^b	(b) (4)	51.00 ^b	(b) (4)	153.00 ^b	(b) (4)	153.00 ^b
Microcrystalline cellulose	NF/Ph. Eur.									
Lactose anhydrous	NF/Ph. Eur.									
Hydroxypropyl cellulose	NF/Ph. Eur.									
Croscarmellose sodium	NF/Ph. Eur.									
Silicified microcrystalline cellulose	NF									
Magnesium stearate ^d	NF/Ph. Eur.									
	(b) (4)									
<i>Metformin HCl XR Layer</i>										
<i>Metformin HCl granulate</i>										
Metformin HCl	Company Specification	Active	(b) (4)	500.00	(b) (4)	1000.00	(b) (4)	500.00	(b) (4)	1000.00
Microcrystalline cellulose	NF/Ph. Eur.									
Hypromellose	(b) (4) USP/Ph. Eur.									
Polyethylene oxide	(b) (4) NF									
	(b) (4) NF									
	USP/Ph. Eur.									
Magnesium stearate ^d	NF/Ph. Eur.									
	(b) (4)									
Component	Quality Reference ^a	Function	50/500 mg (G043)		50/1000 mg (G045)		150/500 mg (G042)		150/1000 mg (G039)	
			%w/w	mg/unit	%w/w	mg/unit	%w/w	mg/unit	%w/w	mg/unit

(Continued)

Film-coating

(b) (4)

4.2. Bioanalytical method validation for quantification of canagliflozin and metformin.

Method Study Location Laboratory	LC-MS/MS NDA204042/Mod5.3.1.4/BA1345 (Partial Validation in K ₂ EDTA)	LC-MS/MS NDA204042/Mod5.3.1.4/PBRL-RD-1092	
		Full Validation for Metformin	Partial Validation Metformin in the Presence of Canagliflozin (b) (4)
Analyte	canagliflozin (JNJ-28431754)	metformin (JNJ-1158196)	metformin (JNJ-1158196)
Matrix	plasma	plasma	plasma
Validated conc range	5.00 to 5,000 ng/mL	5.00 to 2,500 ng/mL	5.00 to 2,500 ng/mL
Dilution integrity	5×	10× and analysis up to 20,000 ng/mL	10× and analysis up to 20,000 ng/mL
Inter-run accuracy (% Bias)	96.9 to 101.9 ^a	-4.3 to -1.1	-1.7 to 4.6 ^c
Inter-run precision (%CV)	0.0 to 4.3	0.0 to 2.6	1.8 to 2.5 ^c
Intra-run accuracy (% Bias)	NA	NA	NA
Intra-run precision (%CV)	0.9 to 3.6	2.3 to 3.9	NA
Intra-run accuracy ([x] × dilution) (% Bias)	95.0 ^a (5× dilution)	-2.5 (10× dilution)	NA
Intra-run precision ([x] × dilution) (%CV)	1.2 (5× dilution)	4.5 (10× dilution)	NA
Selectivity	no relevant interferences ^b	no relevant interferences	no relevant interferences
- Impact of hemolysis	no impact in presence of 2% blood	no impact in presence of 2% blood	N/A
Stability in blood	melting ice: 2 h ^b ; room temp: 2h ^b	0°C: 2 h; room temp: 2 h	0°C: 2 h; room temp: 2 h
Stability in plasma	f-t cycles: 5 ^b ; ultrafreezer: 728 d ^b ; freezer: 728 d ^b ; room temp: 73 h ^b	f-t cycles: 4; ultrafreezer: 190 d; freezer: 190 d; room temp: 26 h	f-t cycles: 5; ultrafreezer: 190 d; freezer: 190 d; room temp: 70 h
Processed sample stability	143 h ^b	191 h (at 10°C)	120 h (at 10°C)
Stability in stock solution:	refrigerator: 20 d; room temp: 27 h	refrigerator: 10 d; room temp: 26 h	NA

conc = concentration, CV = coefficient of variation, f-t = freeze-thaw, NA = not available, SAM = Standard Analytical Method, temp = temperature.

Set temperatures for ultrafreezer: -70°C, freezer: -20°C, refrigerator: 4°C.

^a % accuracy.

^b With and without the presence of metformin.

^c Calculated over the first 5 analytical runs with duplicate quality control samples.

4.3. Individual Study Synopsis

4.3.1. DIA1041 – BE STUDY- 50 mg/500 mg CANA/MET XR FDC

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	To be determined
<u>Name of Active Ingredient(s)</u>	JNJ-28431754 ([Canagliflozin]+JNJ-1158196 [Metformin XR])

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 21 November 2014
Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1041

Title of Study: A Single-Dose, Open-Label, Randomized, 3-Way Crossover Pivotal Study to Assess the Bioequivalence of the Fixed Dose Combination Tablets of Canagliflozin and Metformin Extended Release (XR) (2 x 50 mg/500 mg) With Respect to the Individual Components of Canagliflozin (1 x 100 mg) and Metformin XR Tablet (2 x 500 mg) in Healthy Fed Subjects

NCT No.: NCT02065752

Clinical Registry No.: CR103254

Principal Investigator(s): Danielle Armas, MD

Study Center: Celerion, Inc. 2420 West Baseline Road, Tempe, AZ 85283, USA

Publication (Reference): None

Study Period: 24 February 2014 to 19 April 2014

Phase of Development: 1

Objectives: The primary objectives of this study were:

- To evaluate the bioequivalence of canagliflozin/metformin (CANA/MET) Extended Release (XR) Fixed Dose Combination (FDC) (2 × 50 mg/500 mg tablets; with metformin hydrochloric acid (HCl) granulate manufactured at Gurabo) compared with equal doses of the individual components of canagliflozin (1 x 100 mg tablet) and metformin XR (2 × 500 mg tablets) administered concurrently in healthy fed subjects.
- To evaluate the bioequivalence of CANA/MET XR FDC (2 × 50 mg/500 mg tablets; with metformin HCl granulate manufactured (b) (4) compared with equal doses of the individual components of canagliflozin (1 x 100 mg tablet) and metformin XR (2 × 500 mg tablets) administered concurrently in healthy fed subjects.

The secondary objective was to assess safety and tolerability.

Hypothesis: The FDC tablets of canagliflozin and metformin XR, manufactured with metformin HCl granulate from Gurabo (b) (4) respectively, are bioequivalent to the individual components of canagliflozin and metformin XR at the same dose as determined by the ratio of their geometric means for

AUC and C_{max} values and corresponding 90% confidence intervals (CI) being contained within the 80.00% to 125.00% criteria for bioequivalence.

Methodology: This was a Phase 1, randomized, open-label, single-center, single-dose, 3-treatment, 3-way crossover study in 42 healthy adult subjects. The study consisted of 3 phases: a screening phase of approximately 3 weeks (Days -22 to -2), an open label treatment phase consisting of 3 single-dose treatment periods of 5 days each (Days -1 through 4) separated by a washout of 10 to 14 days between Day 1 of each treatment period, and a follow-up phase occurring 7 to 10 days after the last study-related procedure on Day 4 of Treatment Period 3.

On Day 1 of Treatment Period 1, subjects were randomly assigned to 1 of 6 treatment sequence groups: ABC, ACB, BAC, BCA, CAB, or CBA, where Treatment A (reference) = CANA (1 x 100 mg) + MET XR (2 x 500 mg); Treatment B (Test 1) = CANA/MET XR FDC tablet manufactured at Gurabo (2 x [50 mg/500 mg]); Treatment C (Test 2) = CANA/MET XR FDC tablet manufactured (b) (4) (2 x [50 mg/500 mg]). On Day 1 in each Treatment Period, subjects were to fast from the end of lunch and until the start of dinner (at least 6.5 hours). Thirty minutes before dosing, subjects were given a standardized high-fat dinner meal. Subjects were administered study drug with 240 mL of noncarbonated water 30 minutes after the start of dinner.

Number of Subjects (planned and analyzed): Planned: Approximately 42 subjects were planned to be enrolled to ensure that 36 subjects complete the study.

Analyzed: A total of 42 subjects were enrolled and randomized in this study. A total of 40 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Healthy men and women at least 18 (or the legal age of consent in the jurisdiction in which the study took place) to 55 years of age, inclusive; body mass index (BMI) between 18 and 30 kg/m², inclusive, and a body weight of not less than 50 kg. Systolic blood pressure between 90 and 140 mmHg, and diastolic blood pressure no higher than 90 mmHg with a normal renal function (estimated Glomerular Filtration Rate [eGFR] ≥ 90 mL/min/1.73m² using the Modification of Diet in Renal Disease Study [MDRD] equation), were eligible for enrollment into the study.

Test Product, Dose and Mode of Administration, Batch No.: CANA/MET XR FDC tablets with metformin HCl granulate manufactured at Gurabo, 2 x 50/500 mg tablets; Batch nos: 13JG2572X; Expiry date: July-2014.

CANA/MET XR FDC (b) (4) 2 x 50/500 mg tablets; Batch nos: 13LG3447X; Expiry date: September-2014

Reference Therapy, Dose and Mode of Administration, Batch No.: Canagliflozin 1 x 100 mg tablet; Batch no: 13CG0966X1; Expiry date: April-2016.

GLUMETZA[®] 2 x 500 mg tablets; Batch no: MTBT9431; Expiry date: October-2016

Duration of Treatment: Subjects received single dose of 100 mg CANA and 1000 mg MET XR as separate tablets or single doses of FDC tablets on Day 1 of the 3 treatment periods. The total duration of treatment was for 15 days.

Criteria for Evaluation:

Pharmacokinetics: Based on the individual plasma concentration-time data, using actual sampling times, the following key pharmacokinetic (PK) parameters of canagliflozin and metformin XR were calculated via noncompartmental methods for each treatment: C_{max} , t_{max} , AUC_{last} , AUC_{∞} , $t_{1/2,\lambda z}$.

Safety: Safety and tolerability were evaluated throughout the study and included the collection of adverse events (AEs) including hypoglycemia, subject's physical examination (including height [at screening] and

body weight), evaluation of vital signs (blood pressure, pulse rate and body temperature), 12-lead electrocardiograms (ECGs) and laboratory tests (including hematology, serum chemistry, and urinalysis).

The total amount of blood to be withdrawn for clinical laboratory tests and PK evaluations was approximately 277 mL.

Statistical Methods:

Sample size: The intrasubject coefficients of variation (CV) of AUCs (ie, AUC_{last} and AUC_{∞}) and C_{max} , were estimated to be no more than 22% for canagliflozin and no more than 16% for metformin XR for both the individual tablet and FDC tablet formulations. Assuming the intrasubject CV was the same as the maximum estimated CV of 22% for the PK endpoints of interest (AUCs and C_{max}), a sample size of 36 subjects who completed the study was considered sufficient to conclude bioequivalence of 2×50 mg/500 mg CANA/MET XR FDC tablets compared with the individual components of canagliflozin (1 x 100-mg tablet) and metformin XR (2 x 500 mg tablets) at equal doses with an overall power of 80% (95% power for the individual components), when the between-treatment means differed by 5%.

Pharmacokinetic Analysis:

The statistical analysis was performed on log-transformed estimated PK parameters.

A mixed-effects model that included treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect was used to estimate the least square means and intrasubject variability. Using these estimated least square means and intrasubject variability, 90% CIs for the ratio of geometric mean AUCs and C_{max} for the treatment ratios of B/A and C/A, respectively, were constructed and compared with the 80.00% to 125.00% bioequivalence limits. If the 90% CIs of the ratios fell within these limits, bioequivalence was concluded. If a subject vomited within 24 hours of dosing, the subject's data was excluded from the statistical analyses.

Safety: All subjects who were randomly assigned to treatment and received at least 1 dose of the study drug were included in the safety and tolerability analysis. Baseline values for all laboratory evaluations, vital signs, and 12-lead ECGs were defined as the last evaluation done before study drug administration of each period. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through study completion, including the washout interval.

RESULTS:

STUDY POPULATION:

A total of 42 subjects were enrolled and randomly assigned to 1 of 6 treatment sequences (7 subjects each, in Sequences ABC, ACB, BAC, BCA, CAB, or CBA). Of the 42 enrolled subjects, 40 subjects completed the study. Two subjects discontinued from the study; 1 subject was withdrawn due to an AE (vomiting) and 1 subject withdrew consent from the study prior to PK sample collection at 24 hours in Treatment Period 3 (she received all the 3 treatments). The mean age of the subjects was 37.6 (8.9) years and BMI was 26.43 (2.45) kg/m². Majority of the subjects enrolled were women (69% women vs 31% men) and all subjects were white. Overall, the demographic and baseline characteristics were similar between the 6 treatment sequence groups with slight differences in the mean age, body weight, and eGFR. These were, however, unlikely to affect the safety analysis due to the crossover design of the study.

There were no major protocol deviations in this study that impacted the subject's rights, safety, or well-being or the completeness, accuracy, and reliability of the study data. Overall, all subjects received at least 1 dose of study drug and were included in the safety analysis set.

PHARMACOKINETIC RESULTS:

Forty-two subjects were enrolled, randomized, received study drug, and had PK blood samples obtained. Of the 42 enrolled subjects, 40 subjects completed the study. The dataset used for descriptive statistics included the information available from all subjects. The PK statistical analysis dataset did not include the discontinued subjects.

Canagliflozin

As shown in the tables below, the canagliflozin component of 2 × 50 mg/500 mg FDC tablets (Gurabo manufactured metformin HCl granulate) and 2 × 50 mg/500 mg FDC tablets (b) (4) manufactured metformin HCl granulate) when administered under fed conditions met the predefined BE criteria with respect to AUC_∞, AUC_{last}, and C_{max} relative to 1 × 100 mg canagliflozin + 2 × 500 mg metformin XR tablets, as the 90% CIs for the test-to-reference geometric mean ratios (GMRs) of these parameters were entirely contained within the prespecified BE limits of 80% to 125%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment B vs. Treatment A)

(Study 28431754DIA1041: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 × [50 mg/500 mg]) (Treatment B, Test 1)	CANA (1 x 100 mg) + MET XR (2 × 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	41	924.84	938.84	98.51 (91.46 – 106.10)	20
AUC _{last} (ng.h/mL)	40	9,490.94	9,402.40	100.94 (98.88 – 103.05)	6
AUC _∞ (ng.h/mL)	39	9,707.13	9,601.75	101.10 (99.05 – 103.19)	5

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA (1 x 100 mg) + MET XR [2 × 500 mg]); Test = Treatment B (CANA/MET XR FDC tablet [2 x {50 mg/500 mg}, Gurabo- manufactured metformin HCl granulate])

Key: CI: confidence interval; CV: coefficient variation

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment C vs. Treatment A)

(Study 28431754DIA1041: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 × [50 mg/500 mg]) (Treatment C, Test 2)	CANA (1 x 100 mg) + MET XR (2 × 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	41	889.00	938.84	94.69 (87.91 – 101.99)	20
AUC _{last} (ng.h/mL)	40	9,389.28	9,402.40	99.86 (97.82 – 101.94)	6
AUC _∞ (ng.h/mL)	39	9,597.93	9,601.75	99.96 (97.94 – 102.02)	5

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA [1 x 100 mg] + MET XR [2 × 500 mg]); Test = Treatment C (CANA/MET XR FDC tablet [2 × {50 mg/500 mg}, (b) (4) manufactured metformin HCl granulate])

Key: CI: confidence interval; CV: coefficient variation

Metformin XR

As shown in the tables below, the metformin XR component of 2 × 50 mg/500 mg FDC tablets (Gurabo manufactured metformin HCl granulate) and 2 × 50 mg/500 mg FDC tablets ^{(b) (4)} manufactured metformin HCl granulate) when administered under fed conditions met the predefined BE criteria with respect to AUC_∞, AUC_{last} and C_{max} relative to 1 × 100 mg canagliflozin + 2 × 500 mg metformin XR tablets, as the 90% CIs for the test-to-reference GMRs of these parameters were entirely contained within the prespecified BE limits of 80% to 125%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin XR Pharmacokinetic Parameters (Treatment B vs. Treatment A)

(Study 28431754DIA1041: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [50 mg/500 mg]) (Treatment B, Test 1)	CANA (1 x 100 mg) + MET XR (2 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	41	1,035.23	1,038.15	99.72 (95.03 – 104.63)	13
AUC _{last} (ng.h/mL)	40	11,083.21	11,407.87	97.15 (93.26 – 101.22)	11
AUC _∞ (ng.h/mL)	37	11,286.97	11,492.95	98.21 (94.28 – 102.29)	10

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA [1 x 100 mg] + MET XR [2 x 500 mg]); Test = Treatment B (CANA/MET XR FDC tablet [2 x {50 mg/500 mg}], Gurabo- manufactured metformin HCl granulate)

Key: CI: confidence interval; CV: coefficient variation

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin XR Pharmacokinetic Parameters (Treatment C vs. Treatment A)

(Study 28431754DIA1041: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [50 mg/500 mg]) (Treatment C, Test 2)	CANA (1 x 100 mg) + MET XR (2 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	41	1,073.17	1,038.15	103.37 (98.52 – 108.47)	13
AUC _{last} (ng.h/mL)	40	11,473.72	11,407.87	100.58 (96.54 – 104.78)	11
AUC _∞ (ng.h/mL)	37	11,484.90	11,492.95	99.93 (95.95 – 104.08)	10

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA [1 x 100 mg] + MET XR [2 x 500 mg]); Test = Treatment C (CANA/MET XR FDC tablet [2 x {50 mg/500 mg}] ^{(b) (4)} manufactured metformin HCl granulate)

Key: CI: confidence interval; CV: coefficient variation

SAFETY RESULTS:

Overall across the 3 treatments, 17/42 (40.5%) subjects had 1 or more treatment-emergent adverse events (TEAEs). The most commonly reported TEAEs by system organ class in subjects receiving CANA+MET were seen in gastrointestinal disorders (33.3% [14/42]) followed by general disorders and administration site conditions (11.9% [5/42]) and nervous system disorders (9.5% [4/42]). The most commonly reported TEAEs (≥2 subjects) by preferred term were nausea (n=11), diarrhea (n=8), abdominal pain (n=5), abdominal distension (n=4), postural dizziness (n=3), abdominal pain lower (n=2), flatulence (n=2), chest discomfort (n=2), fatigue (n=2), hyperhidrosis (n=2), and weight decreased (n=2).

There were no deaths or serious adverse events reported during the study. One subject discontinued from the study due to TEAE of vomiting. The investigator assessed the event as mild in severity and very likely related to study drug. The subject also reported other gastrointestinal TEAEs (diarrhea, abdominal pain and nausea) and fatigue and hyperhydrosis. The subject was discontinued from the study due to the event of vomiting on the same day. No treatment was given and the event resolved on the same day.

One subject experienced hypoglycemic event (serum glucose: 2.8 mmol/L, range: 4.16-5.9 mmol/L) on Day 2 Period 3 associated with increased thirst, feeling of generalized weakness, and dizziness. The subject had no past history of hypoglycemic episode. The investigator assessed the event as mild in severity and possibly related to study drug. The subject received graham crackers and Sprite for this event.

Overall, the incidence of TEAEs in subjects was low and similar across all the 3 treatment groups in this crossover study. The majority of the reported TEAEs were assessed by the investigator as mild, with 3 moderate events (nausea, diarrhea, and anxiety). Almost all TEAEs were assessed as being related to study drug either possibly/probably or very likely related to FDC and/or canagliflozin and metformin XR.

Overall, there were no clinically relevant treatment-related changes from baseline at various timepoints of assessments in any of the clinical laboratory analytes (ie, hematology and chemistry). There were no apparent or consistent clinically relevant treatment-related changes from baseline in mean vital sign measurements (systolic and diastolic blood pressure, pulse rate, and body temperature), ECG parameters, or physical examinations.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

- The 2 × 50 mg/500 mg CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2 × 50 mg/500 mg CANA/MET XR FDC tablets containing the (b) (4) manufactured metformin HCl granulate were each bioequivalent to the coadministered 1 × 100 mg canagliflozin and 2 × 500 mg metformin XR tablets in the fed state.
- A single oral dose of 2 × 50 mg/500 mg CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2 × 50 mg/500 mg CANA/MET XR FDC tablets containing the (b) (4) manufactured metformin HCl granulate was well tolerated in healthy adult subjects.

4.3.2. DIA1044 – BE STUDY- 150 mg/1000 mg CANA/MET XR FDC

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	To be determined
<u>Name of Active Ingredient(s)</u>	JNJ-28431754 ([Canagliflozin] + JNJ-1158196 [Metformin XR])

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 15 December 2014
Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1044

Title of Study: A Single-Dose, Open-Label, Randomized, 3-Way Crossover Pivotal Study to Assess the Bioequivalence of the Fixed Dose Combination Tablets of Canagliflozin and Metformin Extended Release (XR) (2 x 150 mg/1,000 mg) With Respect to the Individual Components of Canagliflozin (1 x 300 mg) and Metformin XR Tablet (4 x 500 mg) in Healthy Fed Subjects

NCT No.: NCT02073227

Clinical Registry No.: CR103256

Principal Investigator(s): Danielle Armas, MD

Study Center(s): Celerion, Inc., 2420 West Baseline Road, Tempe, AZ 85283, USA

Publication (Reference): None

Study Period: 17 March 2014 to 21 June 2014, Database Lock: 31 July 2014

Phase of Development: 1

Objectives: The primary objectives of this study were:

- To evaluate the bioequivalence (BE) of canagliflozin/metformin (CANA/MET) extended release (XR) fixed dose combination (FDC; 2 x [150 mg/1,000 mg] tablets; with metformin HCl granulate manufactured at Gurabo) compared with equal doses of the individual components of canagliflozin (1 x 300-mg tablet) and metformin XR (4 x 500-mg tablets) administered concurrently in healthy fed subjects.
- To evaluate the BE of CANA/MET XR FDC (2 x [150 mg/1,000 mg] tablets; with metformin HCl granulate manufactured (b)(4) compared with equal doses of the individual components of canagliflozin (1 x 300-mg tablet) and metformin XR (4 x 500-mg tablets) administered concurrently in healthy fed subjects.

The secondary objectives were to assess safety and tolerability of the 3 treatments.

Hypothesis: The FDC tablets of canagliflozin and metformin XR, manufactured with metformin HCl granulate from Gurabo (b)(4) respectively, are bioequivalent to the individual components of canagliflozin and metformin XR at the same dose as determined by the ratio of their geometric means for AUC and C_{max} values and corresponding 90% confidence intervals (CIs) being contained within the 80.00% to 125.00% criteria for BE.

Methodology: This was a randomized, open-label, single-center, single-dose, 3-treatment, 3-way crossover study planned for approximately 42 healthy adult subjects. The study consisted of 3 phases: a screening phase of approximately 3 weeks (Days -22 to -2), an open-label treatment phase consisting of 3 single-dose treatment periods of 5 days each (Days -1 through 4) separated by a washout of 10 to 14 days between Day 1 of each treatment period, and a follow-up phase occurring 7 to 10 days after the last study-related procedure on Day 4 of Treatment Period 3.

On Day 1 of Treatment Period 1, subjects were randomly assigned to 1 of 6 treatment sequence groups (ABC, ACB, BAC, BCA, CAB, or CBA).

- Treatment A (reference) = CANA (1 x 300 mg) + MET XR (4 x 500 mg)
- Treatment B (Test 1, metformin HCl granulate manufactured at Gurabo) = CANA/MET XR FDC tablet (2 x [150 mg/1,000 mg])
- Treatment C (Test 2, metformin HCl granulate manufactured (b)(4)) = CANA/MET XR FDC tablet (2 x [150 mg/1,000 mg]).

On Day 1 in each treatment period, subjects fasted from the end of lunch and until the start of dinner (at least 6.5 hours). Thirty minutes before dosing, subjects were given a standardized high-fat dinner meal. Subjects were administered study drug with 240 mL of noncarbonated water 30 minutes after the start of dinner.

Number of Subjects (planned and analyzed):

Planned: Approximately 42 subjects were planned to be enrolled to ensure that 36 subjects completed the study.

Analyzed: A total of 52 subjects were enrolled in the study; out of which 39 subjects completed the study. All subjects who received at least 1 dose of the study drug were included in the safety and tolerability analysis (n=51).

Diagnosis and Main Criteria for Inclusion: Healthy men and women at least 18 years (or the legal age of consent in the jurisdiction in which the study took place) to 55 years of age, inclusive; body mass index (BMI) between 18 kg/m² and 30 kg/m², inclusive, and a body weight of not less than 50 kg. Blood pressure between 90 mmHg and 140 mmHg (inclusive), systolic, and no higher than 90 mmHg diastolic with normal renal function (estimated Glomerular Filtration Rate [eGFR] ≥90 mL/min/1.73m² using the Modification of Diet in Renal Disease Study equation), were eligible for enrollment into the study.

Test Product, Dose and Mode of Administration, Batch No.: CANA/MET XR FDC tablets (Gurabo manufactured metformin HCl granulate), 2 x (150/1,000 mg) tablets, oral. Batch No.: 13JG2578X; Expiration date: July 2014.

CANA/MET XR FDC tablets (b)(4) manufactured metformin HCl granulate), 2 X (150/1,000 mg) tablets, oral. Batch No.: 13LG3450X; Expiration date: September 2014.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Canagliflozin tablets 1 X 300-mg, oral, Batch No.: 13AG0462X; Expiration Date: February 2016.

GLUMETZA[®] tablets 4 X 500-mg, oral, Batch No.: MTBT9431; Expiration Date: October 2016.

Duration of Treatment: Subjects received a single dose of 300 mg CANA and 2,000 mg MET XR either as separate tablets or FDC tablets on Day 1 of the 3 treatment periods. The planned study duration was approximately 70 days.

Criteria for Evaluation:

Pharmacokinetics: Based on the individual plasma concentration-time data, using actual sampling times, the following key pharmacokinetic (PK) parameters of canagliflozin and metformin were calculated via noncompartmental methods for each treatment: $C_{\max}$, $t_{\max}$, AUC_{last} , AUC_{∞} and $t_{1/2,\lambda z}$.

Safety: Safety and tolerability were evaluated throughout the study and included the collection of treatment-emergent adverse events (TEAEs) including hypoglycemia, subject's physical examination (including height [at screening] and body weight), evaluation of vital signs (blood pressure, pulse rate and body temperature), 12-lead electrocardiograms (ECGs) and laboratory tests (including hematology, serum chemistry, and urinalysis).

The total amount of blood to be drawn for clinical laboratory tests and PK evaluations was approximately 277 mL per subject.

Statistical Methods:

Sample size: The intrasubject coefficients of variation (CV) of AUCs (ie, AUC_{last} and AUC_{∞}) and $C_{\max}$ were estimated to be no more than 22% for canagliflozin and no more than 16% for metformin XR for both the individual tablet and FDC tablet formulations. Assuming the intrasubject CV was the same as the maximum estimated CV of 22% for the PK endpoints of interest (AUCs and $C_{\max}$), a sample size of 36 subjects who completed the study was considered sufficient to conclude BE of 2 x (150 mg/1,000 mg) CANA/MET XR FDC tablets, respectively, compared with the individual components of canagliflozin (1 x 300-mg tablet) and metformin XR (4 x 500-mg tablets) at equal doses with an overall power of 80% (95% power for the individual components), when the between-treatment means differed by 5%.

Pharmacokinetic Analysis: Individual and mean canagliflozin and metformin plasma concentration-time profiles were plotted for each treatment. Plasma concentration data at each timepoint were summarized with mean, median, minimum, maximum, standard deviation (SD), and CV% for each treatment. All PK parameters of canagliflozin and metformin were summarized with mean, median, geometric mean, minimum value, maximum value, SD, and CV% by treatment.

The statistical analysis was performed on log-transformed PK parameters.

A mixed-effects model that included treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect was used to estimate the least square means and intrasubject variability. Using these estimated least square means and intrasubject variability, 90% CIs for the ratio of geometric mean AUCs and $C_{\max}$ for the treatment ratios of B/A and C/A, respectively, were constructed and compared with the 80.00% to 125.00% BE limits. If the 90% CIs of the ratios fell within these limits, BE was concluded. If a subject vomited within 24 hours of dosing, the subject's data were excluded from the statistical analyses.

Safety: All subjects who were randomly assigned to treatment and received at least 1 dose of the study drug were included in the safety and tolerability analysis. Baseline values for all laboratory evaluations, vital signs, and 12-lead ECGs were defined as the last evaluation done before study drug administration of each period. Safety was evaluated by examining the incidence and type of adverse events (AEs), and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through study completion, including the washout interval.

RESULTS:

STUDY POPULATION

A total of 52 subjects were enrolled and randomly assigned to 1 of the 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA). Of the 52 subjects, 51 subjects received at least one dose of study drug (one subject was not able to swallow the study drug and was withdrawn from the study) and 39 subjects completed the study. Twelve subjects were prematurely withdrawn from the study: 6 due to a protocol violation, 3 due to an AE, 2 due to withdrawal of consent, and 1 due to other reasons. The median age of the subjects was 37.0 years (range: 18 to 55 years) and mean (SD) BMI was 25.7 (2.6) kg/m². Nearly all subjects were white (98%) and the majority were Hispanic (75%). Overall, the demographic and baseline characteristics were generally similar between the 6 treatment sequence groups.

PHARMACOKINETIC RESULTS:

Fifty-two subjects were enrolled and randomized in the study; of the 52 randomized subjects, 51 subjects received study drug, and had PK blood samples obtained during the study, and 39 subjects completed the study. The dataset used for descriptive statistics included the information available from all subjects with estimable data. The statistical analysis was performed on log-transformed PK parameters. Only the data from subjects who had evaluable PK for all 3 Treatment Periods were included in the statistical analysis.

Canagliflozin

As shown in tables below, the canagliflozin component of the 150 mg/1000 mg FDC tablet (Gurabo manufactured metformin HCl granulate) and the 150 mg/1000 mg FDC tablet ^{(b)(4)} manufactured metformin HCl granulate), when administered as 2 tablets under fed conditions, met the predefined BE criteria with respect to AUC_∞, AUC_{last}, and C_{max} relative to 1 x 300 mg canagliflozin + 4 x 500 mg metformin XR tablets as the 90% CIs for the test-to-reference geometric mean ratios of these parameters were entirely contained within the prespecified BE limits of 80.00% to 125.00%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment B vs. Treatment A) (Study 28431754DIA1044: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/1000 mg]) (Treatment B, Test 1)	CANA (1 x 300 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	39	2855.66	3095.73	92.25 (85.49-99.54)	20
AUC _{last} (ng.h/mL)	39	29439.20	30168.27	97.58 (95.74-99.46)	5
AUC _∞ (ng.h/mL)	37	30622.31	31383.57	97.57 (95.64-99.55)	5

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Key: CANA=canagliflozin; CI=confidence interval; CV=coefficient of variation; FDC=fixed dose combination; MET=metformin; vs.=versus; XR=extended release

Reference = Treatment A (CANA [1 x 300 mg] + MET XR [4 x 500 mg]); Test = Treatment B (CANA/MET XR FDC tablet [2 x {150 mg/1000 mg}]; Gurabo-manufactured metformin HCl granulate)

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment C vs. Treatment A)
(Study 28431754DIA1044: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/1000 mg]) (Treatment C, Test 2)	CANA (1 x 300 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	39	2837.95	3095.73	91.67 (84.96-98.91)	20
AUC _{last} (ng.h/mL)	39	29136.75	30168.27	96.58 (94.76-98.43)	5
AUC _∞ (ng.h/mL)	37	30306.38	31383.57	96.57 (94.66-98.52)	5

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Key: CANA=canagliflozin; CI=confidence interval; CV=coefficient of variation; FDC=fixed dose combination; MET=metformin; vs.=versus; XR=extended release

Reference = Treatment A (CANA [1 x 300 mg] + MET XR [4 x 500 mg]); Test = Treatment C (CANA/MET XR FDC tablet [2 x {150 mg/1000 mg}]; ^{(b) (4)}Manufactured Metformin HCl Granulate)

Metformin XR

As shown in tables below, the metformin component of the 150 mg/1000 mg FDC tablet (Gurabo manufactured metformin HCl granulate) and the 150 mg/1000 mg FDC tablet ^{(b) (4)}manufactured metformin HCl granulate), when administered as 2 tablets under fed conditions, met the predefined BE criteria with respect to AUC_∞, AUC_{last}, and C_{max} relative to 1 x 300 mg canagliflozin + 4 x 500 mg metformin XR tablets as the 90% CIs for the test-to-reference geometric mean ratios of these parameters were entirely contained within the prespecified BE limits of 80.00% to 125.00%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin Pharmacokinetic Parameters (Treatment B vs. Treatment A)
(Study 28431754DIA1044: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/1000 mg]) (Treatment B, Test 1)	CANA (1 x 300 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	36	2203.80	2078.27	106.04 (101.29-111.02)	12
AUC _{last} (ng.h/mL)	36	24135.29	24155.57	99.92 (96.08-103.91)	10
AUC _∞ (ng.h/mL)	32	24843.07	24249.95	102.45 (98.67-106.37)	9

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Key: CANA=canagliflozin; CI=confidence interval; CV=coefficient of variation; FDC=fixed dose combination; MET=metformin; vs.=versus; XR=extended release

Reference = Treatment A (CANA [1 x 300 mg] + MET XR [4 x 500 mg]); Test = Treatment B (CANA/MET XR FDC tablet [2 x {150 mg/1000 mg}]; Gurabo- Manufactured Metformin HCl Granulate)

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin Pharmacokinetic Parameters (Treatment C vs. Treatment A)
(Study 28431754DIA1044: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/1000 mg]) (Treatment C, Test 2)	CANA (1 x 300 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	36	2194.97	2078.27	105.62 (100.89-110.56)	12
AUC _{last} (ng.h/mL)	36	24236.89	24155.57	100.34 (96.49-104.34)	10
AUC _∞ (ng.h/mL)	32	24666.84	24249.95	101.72 (97.94-105.64)	9

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Key: CANA=canagliflozin; CI=confidence interval; CV=coefficient of variation; FDC=fixed dose combination; MET=metformin; vs.=versus; XR=extended release

Reference = Treatment A (CANA [1 x 300 mg] + MET XR [4 x 500 mg]); Test = Treatment C (CANA/MET XR FDC tablet [2 x {150 mg/1000 mg}]; (b)(4) Manufactured Metformin HCl Granulate)

SAFETY RESULTS:

There were no deaths, serious adverse events, or persistent AEs reported during the study. Three subjects were withdrawn from the study due to a TEAE (ie, vomiting and retching) which was a pre-specified withdrawal criterion.

Overall across the 3 treatments, 49.0% (25/51) subjects reported at least 1 or more TEAEs. The most commonly reported TEAEs by system organ class (SOC) were in nervous system disorder (33.3% [17/51]) followed by gastrointestinal disorders (25.5% [13/51]), and general disorders and administration site conditions (13.7% [7/51]). The most common reported TEAEs (n ≥ 3 subjects) by preferred term were headache (19.6% [10/51]), nausea (19.6% [10/51]), diarrhea (9.8% [5/51]), and postural dizziness, paraesthesia, presyncope, syncope, abdominal distension, abdominal pain, constipation, and ocular hyperemia (each 5.9% [3/51]).

Overall, the incidence of TEAEs in subjects was similar across all the 3 treatment sequences in this crossover study (Treatment A 29.2% [14/48], Treatment B 27.7% [13/47] and Treatment C 29.5% [13/44]).

All the reported TEAEs were mild or moderate in severity except for 1 severe event of headache observed after receiving Treatment B. In addition, all reported TEAEs were transient and resolved by the end of the study.

The majority of TEAEs were assessed as not related or possibly related to any of the study drugs by the investigator with only few events being doubtfully or probably related. The TEAEs which were assessed as very likely related to any of the study drugs belonged to the gastrointestinal disorders SOC followed by the nervous system disorder SOC. In Treatment A, the events which were considered as very likely related to canagliflozin were: nausea (n=5), postural dizziness, dizziness, and constipation (each n=1). The events which were considered as very likely related to metformin were: nausea (n=5), diarrhea (n=2), and abdominal pain (n=1). In Treatment B, the events which were considered as very likely related to study drug were: nausea (n=4), diarrhea (n=2), abdominal pain, vomiting, and presyncope (each n=1). In Treatment C, the events which were considered as very likely related to study drug were: diarrhea (n=2), nausea, abdominal distension, and constipation (each n=1).

Overall, there were no clinically meaningful treatment-related changes from baseline at various timepoints of assessments in any of the clinical laboratory analytes (ie, hematology, chemistry, and

urinalysis). There were no clinically meaningful changes or consistent treatment-related changes from baseline in mean vital sign measurements (systolic and diastolic blood pressure, pulse rate, and body temperature), ECG parameters, or physical examinations.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- The 2 × (150 mg/1000 mg) CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2 × (150 mg/1000 mg) CANA/MET XR FDC tablets containing the (b)(4) manufactured metformin HCl granulate were each bioequivalent to the coadministered 1 × 300 mg canagliflozin and 4 × 500 mg metformin XR tablets in the fed state with respect to C_{max} and AUCs for both canagliflozin and metformin.

The 2 × (150 mg/1,000 mg) CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2 × (150 mg/1,000 mg) CANA/MET XR FDC tablets containing the (b)(4) manufactured metformin HCl granulate were safe and well tolerated with no new, unexpected, or unusual safety signals.

APPEARS THIS WAY ON ORIGINAL

4.3.3. DIA1062 – BE STUDY- 50 mg/1000 mg CANA/MET XR FDC

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	To be determined
<u>Name of Active Ingredient(s)</u>	JNJ-28431754 ([[Canagliflozin]+JNJ-1158196 [Metformin XR]])

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 1 December 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1062

Title of Study: A Single-Dose, Open-Label, Randomized, 3-Way Crossover Pivotal Study to Assess the Bioequivalence of the Fixed Dose Combination Tablets of Canagliflozin and Metformin Extended Release (XR) (2 x 50 mg/1,000 mg) With Respect to the Individual Components of Canagliflozin (1 x 100 mg) and Metformin XR Tablet (4 x 500 mg) in Healthy Fed Subjects

NCT No.: NCT02077803

Clinical Registry No.: CR103257

Principal Investigator(s): Danielle Armas, MD, Celerion Inc., 2420 West baseline Road, Tempe, AZ 85283, USA

Study Center(s): Celerion, Phx, AZ 85283, USA

Publication (Reference): None

Study Period: 17 March 2014 to 01 July 2014. Database Lock – 25 July 2014

Phase of Development: 1

Objectives: The primary objectives of this study were:

- To evaluate the bioequivalence of canagliflozin/metformin (CANA/MET) extended release (XR) fixed dose combination (FDC) (2 x 50 mg/1,000 mg tablets; with metformin HCl granulate manufactured at Gurabo) compared with equal doses of the individual components of canagliflozin (1 x 100 mg tablet) and metformin XR (MET XR) (4 x 500 mg tablets) administered concurrently in healthy fed subjects.
- To evaluate the bioequivalence of canagliflozin/metformin (CANA/MET) XR FDC (2 x 50 mg/1,000 mg tablets; with metformin HCl granulate manufactured (b)(4) compared with equal doses of the individual components of canagliflozin (1 x 100 mg tablet) and MET XR (4 x 500 mg tablets) administered concurrently in healthy fed subjects.

The secondary objectives were to assess safety and tolerability of the three treatments regimens.

Hypothesis: The FDC tablets of canagliflozin and MET XR, manufactured with metformin HCl granulate from Gurabo (b)(4) are bioequivalent to the individual components of

canagliflozin and MET XR at the same dose as determined by the ratio of their geometric means for AUC and C_{max} values and corresponding 90% confidence intervals (CIs) being contained within the 80.00% to 125.00% criteria for bioequivalence.

Methodology: This was a randomized, open-label, single-center, single-dose, 3-treatment, 3-way crossover study planned in 42 healthy adult subjects. The study consisted of 3 phases: a screening phase of approximately 3 weeks (Days -22 to -2), an open label treatment phase consisting of 3 single-dose treatment periods of 5 days each (Days -1 through 4) separated by a washout of 10 to 14 days between Day 1 of each treatment period, and a follow-up phase occurring 7 to 10 days after the last study-related procedure on Day 4 of Treatment Period 3. On Day 1 of Treatment Period 1, subjects were randomly assigned to 1 of 6 treatment sequence groups (ABC, ACB, BAC, BCA, CAB, or CBA).

On Day 1 in each Treatment Period, subjects fasted from the end of lunch and until the start of dinner (at least 6.5 hours). Thirty minutes before dosing, subjects were given a standardized high-fat dinner meal. Subjects were administered study drug with 240 mL of noncarbonated water 30 minutes after the start of dinner. Liquids were not allowed beginning 1 hour before the dinner to 1 hour after study drug administration, with the exception of liquids supplied with dinner and the water supplied at dosing. Subjects remained in an upright position from study drug administration until 4 hours afterward. Study staff monitored fasting glucose via fingerstick while subjects were confined to the study center.

Number of Subjects (planned and analyzed): Planned: Approximately 42 subjects were planned to be enrolled to ensure that 36 subjects completed the study.

Analyzed: A total of 47 subjects were enrolled and randomly assigned to 1 of 6 treatment sequences ABC (n=8), ACB (n=9), BAC (n=8), BCA (n=7), CAB (n=8), and CBA (n=7) as shown in the table below. Of the 47 randomized subjects, 39 subjects completed the study and 8 subjects discontinued from the study.

Diagnosis and Main Criteria for Inclusion: Healthy men and women at least 18 (or the legal age of consent in the jurisdiction in which the study took place) to 55 years of age, inclusive; body mass index (BMI) between 18 and 30 kg/m², inclusive, and a body weight of not less than 50 kg. Blood pressure between 90 and 140 mmHg (inclusive), systolic, and no higher than 90 mmHg diastolic with a normal renal function (estimated Glomerular Filtration Rate [eGFR] ≥ 90 mL/min/1.73m² using the Modification of Diet in Renal Disease Study [MDRD] equation), were eligible for enrollment into the study.

Test Product, Dose and Mode of Administration, Batch No.: CANA/MET XR FDC were supplied as a 2 x 50/1,000 mg oral tablets, Gurabo Batch no: 13JG2668X (Expiry date: July 2014) and ^{(b)(4)} Batch no: 13LG3448X (Expiry date: September 2014).

Reference Therapy, Dose and Mode of Administration, Batch No.: Canagliflozin was supplied as 1 x 100 mg oral tablets, Batch no: 13CG0966X1; Expiry date: April 2016.

GLUMETZA® was supplied as 4 x 500 mg oral tablets, Batch no: MTBT9431; Expiry date: October 2016.

Duration of Treatment: The study consisted of 3 phases: a screening phase of approximately 3 weeks, an open label treatment phase consisting of 3 single-dose treatment periods of 5 days each separated by a washout of 10 to 14 days between Day 1 of each treatment period, and a follow-up phase occurring 7 to 10 days after the last study-related procedure on Day 4 of Treatment Period 3. The planned total study duration was approximately 70 days.

Criteria for Evaluation:

Pharmacokinetics: Based on the individual plasma concentration-time data, using actual sampling times, the following key pharmacokinetic (PK) parameters of canagliflozin and MET XR were calculated via noncompartmental methods for each treatment: C_{max} , t_{max} , AUC_{last} , AUC_{∞} and $t_{1/2,\lambda z}$.

Safety: Safety and tolerability were evaluated throughout the study and included the collection of adverse events (AEs) including hypoglycemia, subject's physical examination (including height [at screening] and body weight), evaluation of vital signs (blood pressure, pulse rate and body temperature), 12-lead electrocardiograms (ECGs) and laboratory tests (including hematology, serum chemistry, and urinalysis).

Statistical Methods:

Sample size: The intrasubject coefficients of variation (CV) of AUCs (ie, AUC_{last} and AUC_{∞}) and C_{max} , respectively, were estimated to be no more than 22% for canagliflozin and no more than 16% for MET XR for both the individual tablet and FDC tablet formulations. Assuming the intrasubject CV was the same as the maximum estimated CV of 22% for the pharmacokinetic (PK) endpoints of interest (AUCs and C_{max}), a sample size of 36 subjects who completed the study was considered sufficient to conclude bioequivalence of 2 x 50 mg/1,000 mg CANA/MET XR FDC tablets, respectively, compared with the individual components of canagliflozin (1 x 100 mg tablet) and MET XR (4 x 500 mg tablets) at equal doses with an overall power of 80% (95% power for the individual components), when the between-treatment means differed by 5%.

Pharmacokinetic Analysis: Individual and mean canagliflozin and MET XR plasma concentration-time profiles were plotted for each treatment. Plasma concentration data at each time point were summarized with mean, median, minimum, maximum, standard deviation (SD), and CV% for each treatment. All PK parameters of canagliflozin and MET XR were summarized with mean, median, geometric mean, minimum value, maximum value, SD, and CV% by treatment.

The statistical analysis was performed on log-transformed pharmacokinetic parameters.

A mixed-effects model that included treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect was used to estimate the least square means and intrasubject variability. Using these estimated least square means and intrasubject variability, 90% confidence intervals (CIs) for the ratio of geometric mean AUCs and C_{max} for the treatment ratios of B/A and C/A, respectively, were constructed and compared with the 80.0% to 125.0% bioequivalence limits. If the 90% CIs of the ratios fell within these limits, bioequivalence was concluded. If a subject vomited within 24 hours of dosing, the subject's data was excluded from the statistical analyses of PK parameters.

Safety: All subjects who were randomly assigned to treatment and received at least 1 dose of the study drug were included in the safety and tolerability analysis. Baseline values for all laboratory evaluations, vital signs, and 12-lead ECGs were defined as the last evaluation done before study drug administration of each period. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through study completion, including the washout interval.

RESULTS:

STUDY POPULATION: A total of 47 subjects were enrolled and randomly assigned to 1 of 6 treatment sequences (ABC [n=8], ACB [n=9], BAC [n=8], BCA [n=7], CAB [n=8], and CBA [n=7]). Of the 47 randomized subjects, 39 subjects completed the study. Eight subjects discontinued from the study due to adverse event (n=4), and withdrawal of consent by subject (n=1). Three subjects withdrew due to protocol violations (which are included among the protocol deviations). Three subjects reported of the following major protocol deviations during the study: 2 subjects had vomiting within 24 hours of dosing and were not included in the descriptive statistics; another subject did not have PK sample drawn due to difficult venipuncture.

The baseline median age of the subjects was 33 years (range: 18 to 55 years), mean (SD) BMI was 25.5 kg/m² (2.8 kg/m²), mean (SD) body weight was 67.2 kg (9.6 kg). The majority of the subjects were white (85%). Overall, the demographic and baseline characteristics were comparable among the 6 treatment sequence groups.

PHARMACOKINETIC RESULTS:

Forty-seven subjects were enrolled, randomized, received study drug, and had PK blood samples obtained. Of the 47 randomized subjects, 39 subjects completed the study. The dataset used for descriptive statistics included the information available from all subjects. The pharmacokinetic statistical analysis dataset did not include the discontinued subjects and subjects who had missing PK parameters for other reasons.

Canagliflozin

As shown in the tables below, the canagliflozin component of the 50 mg/1,000 mg FDC tablet (Gurabo manufactured metformin HCl granulate) and the 50 mg/1,000 mg FDC tablet ^{(b)(4)} manufactured metformin HCl granulate), when administered as 2 tablets under fed conditions met the predefined bioequivalence (BE) criteria with respect to AUC_{∞} , AUC_{last} , and C_{max} relative to 1 x 100 mg canagliflozin + 4 x 500 mg MET XR tablets as the 90% CIs for the test-to-reference geometric mean ratios (GMRs) of these parameters were entirely contained within the prespecified BE limits of 80.0% to 125.0%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment B vs. Treatment A) (Study 28431754DIA1062: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [50 mg/1,000 mg]) (Treatment B, Test 1)	CANA (1 x 100 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C_{max} (ng/mL)	38	889.55	962.11	92.46 (86.10 – 99.28)	6
AUC_{last} (ng.h/mL)	38	9,367.97	10,008.70	93.60 (91.43 – 95.81)	6
AUC_{∞} (ng.h/mL)	36	9,652.16	10,317.39	93.55 (91.25 – 95.91)	19

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms
Reference = Treatment A (CANA (1 x 100 mg) + MET XR [4 x 500 mg]); Test = Treatment B (CANA/MET XR FDC tablet [2 x {50 mg/1,000 mg}], Gurabo- manufactured metformin HCl granulate)
Key: CI: confidence interval; CV: coefficient variation

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment C vs. Treatment A) (Study 28431754DIA1062: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [50 mg/1,000 mg]) (Treatment C, Test 2)	CANA (1 x 100 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C_{max} (ng/mL)	38	983.12	962.11	102.18 (95.15 – 109.73)	19
AUC_{last} (ng.h/mL)	38	9,987.69	10,008.70	99.79 (97.48 – 102.15)	6
AUC_{∞} (ng.h/mL)	36	10,256.01	10,317.39	99.41 (96.97 – 101.91)	6

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms
Reference = Treatment A (CANA [1 x 100 mg] + MET XR [4 x 500 mg]); Test = Treatment C (CANA/MET XR FDC tablet [2 x {50 mg/1,000 mg}] ^{(b)(4)} manufactured metformin HCl granulate)
Key: CI: confidence interval; CV: coefficient variation

Metformin XR

As shown in the tables below, the MET XR component of the 50 mg/1,000 mg FDC tablet (Gurabo manufactured metformin HCl granulate) and the 50 mg/1,000 mg FDC tablet ^{(b)(4)} manufactured metformin HCl granulate) when administered as 2 tablets under fed conditions, met the predefined BE criteria with respect to AUC_{∞} , AUC_{last} and C_{max} relative to 1 x 100 mg canagliflozin + 4 x 500 mg MET XR tablets as the 90% CIs for the test-to-reference GMRs of these parameters were entirely contained within the prespecified BE limits of 80.0% to 125.0%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin Pharmacokinetic Parameters (Treatment B vs. Treatment A)
(Study 28431754DIA1062: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [50 mg/1,000 mg]) (Treatment B, Test 1)	CANA (1 x 100 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	38	2,203.55	2,104.86	104.69 (99.55 – 110.09)	13
AUC _{last} (ng.h/mL)	38	26,102.76	25,483.73	102.43 (97.64 – 107.46)	13
AUC _∞ (ng.h/mL)	36	26,539.77	25,841.88	102.70 (97.61 – 108.05)	13

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms
Reference = Treatment A (CANA [1 x 100 mg] + MET XR [4 x 500 mg]); Test = Treatment B (CANA/MET XR FDC tablet [2 x {50 mg/1,0900 mg}, Gurabo- manufactured metformin HCl granulate])
Key: CI: confidence interval; CV: coefficient variation

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin Pharmacokinetic Parameters (Treatment C vs. Treatment A)
(Study 28431754DIA1062: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [50 mg/1,000 mg]) (Treatment C, Test 2)	CANA (1 x 100 mg) + MET XR (4 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	38	2,204.62	2,104.86	104.74 (99.59 – 110.15)	13
AUC _{last} (ng.h/mL)	38	25,523.66	25,483.73	100.16 (95.47 – 105.08)	13
AUC _∞ (ng.h/mL)	36	25,990.22	25,841.88	100.57 (95.58 – 105.83)	13

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms
Reference = Treatment A (CANA [1 x 100 mg] + MET XR [4 x 500 mg]); Test = Treatment C (CANA/MET XR FDC tablet [2 x {50 mg/1,000 mg}, ^{(b)(4)}manufactured metformin HCl granulate])
Key: CI: confidence interval; CV: coefficient variation

SAFETY RESULTS: There were no deaths, serious adverse events, or persistent adverse events reported during the study. Three subjects discontinued from the study due to the treatment-emergent adverse event (TEAE) of vomiting and 1 subject due to the TEAE of blood pressure increased. The most commonly reported TEAEs by SOC were in gastrointestinal disorders (59.6% [28/47]) followed by nervous system disorders (36.2% [17/47]). The most commonly reported TEAEs (>2 subjects) by preferred term were nausea (n=22), diarrhea (n=10), vomiting (n=5), abdominal distension (n=3), headache (n=9), dizziness postural (n=7), somnolence (n=4), decreased appetite (n=4), and anxiety (n=3). All of the reported TEAEs were considered as mild or moderate in severity. Almost all the TEAEs including gastrointestinal TEAEs were assessed as related to one of the study drugs (either very likely or possibly/probably related to study drug, with only few events being doubtfully or not related). All the reported TEAEs were resolved by the end of the study.

Overall, there were no clinically meaningful treatment-related changes from baseline at various time points of assessments in any of the clinical laboratory analytes (ie, hematology and chemistry). There were no apparent or consistent treatment-related changes from baseline in mean vital sign measurements (systolic and diastolic blood pressure, pulse rate, and body temperature), ECG parameters, or physical examinations.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

- The 2 x 50 mg/1,000 mg CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2 x 50 mg/1,000 mg CANA/MET XR FDC tablets containing the (b)(4) manufactured metformin HCl granulate were each bioequivalent to the coadministered 1 x 100 mg canagliflozin and 4 x 500 mg MET XR tablets in the fed state with respect to C_{max} and AUCs for both canagliflozin and metformin.
- The 2 x 50 mg/1,000 mg CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2 x 50 mg/1,000 mg CANA/MET XR FDC tablets containing the (b)(4) manufactured metformin HCl granulate were safe and well tolerated with no new, unexpected, or unusual safety signals.

APPEARS THIS WAY ON ORIGINAL

4.3.4. DIA1063 – BE STUDY- 150 mg/500 mg CANA/MET XR FDC

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	To be determined
<u>Name of Active Ingredient(s)</u>	JNJ-28431754 ([[Canagliflozin] + JNJ-1158196 [Metformin XR]])

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 13 November 2014
Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1063

Title of Study: A Single-Dose, Open-Label, Randomized, 3-Way Crossover Pivotal Study to Assess the Bioequivalence of the Fixed Dose Combination Tablets of Canagliflozin and Metformin Extended Release (XR) (2 x 150 mg/500 mg) With Respect to the Individual Components of Canagliflozin (1 x 300 mg) and Metformin XR Tablet (2 x 500 mg) in Healthy Fed Subjects

NCT No.: NCT02071368

Clinical Registry No.: CR103258

Principal Investigator(s): Danielle Armas, MD

Study Center(s): Celerion, Inc. 2420 West Baseline Road, Tempe, AZ 85283, USA

Publication (Reference): None

Study Period: 24 February 2014 to 28 May 2014

Phase of Development: 1

Objectives: The primary objectives of this study were:

- To evaluate the bioequivalence of canagliflozin/metformin (CANA/MET) XR fixed dose combination (FDC) (2×150 mg/500 mg tablets; with metformin HCl granulate manufactured at Gurabo) compared with equal doses of the individual components of canagliflozin (1×300-mg tablet) and metformin XR (2×500-mg tablets) administered concurrently in healthy fed subjects.
- To evaluate the bioequivalence of canagliflozin/metformin (CANA/MET) XR FDC (2×150 mg/500 mg tablets; with metformin HCl granulate manufactured (b)(4)) compared with equal doses of the individual components of canagliflozin (1×300-mg tablet) and metformin XR (2×500-mg tablets) administered concurrently in healthy fed subjects.

The secondary objective was to assess safety and tolerability.

Hypothesis: The FDC tablets of canagliflozin and metformin XR, manufactured with metformin HCl granulate from Gurabo (b)(4) are bioequivalent to the individual components of canagliflozin and metformin XR at the same dose as determined by the ratio of their geometric means for

AUC and C_{max} values and corresponding 90% confidence intervals (CIs) being contained within the 80.00% to 125.00% criteria for bioequivalence.

Methodology: This was a phase 1, randomized, open-label, single-center, single-dose, 3-treatment, 3-way crossover study in 42 healthy adult subjects. The study consisted of 3 phases: a screening phase of approximately 3 weeks (Days -22 to -2), an open label treatment phase consisting of 3 single-dose treatment periods of 5 days each (Days -1 through 4) separated by a washout of 10 to 14 days between Day 1 of each treatment period, and a follow-up phase occurring 7 to 10 days after the last study-related procedure on Day 4 of Treatment Period 3.

On Day 1 of Treatment Period 1, subjects were randomly assigned to 1 of 6 treatment sequence groups (ABC, ACB, BAC, BCA, CAB, or CBA; where Treatment A=1 canagliflozin 300-mg tablet with 2 metformin XR 500-mg tablets [Reference], Treatment B=2 CANA/MET XR FDC 150-mg/500-mg tablets with metformin HCl granulate manufactured at Gurabo [Test 1] and Treatment C=2 CANA/MET XR FDC 150-mg/500-mg tablets with metformin HCl granulate manufactured (b)(4) [Test 2]).

On Day 1 in each Treatment Period, subjects were made to fast from the end of lunch and until the start of dinner (at least 6.5 hours). Thirty minutes before dosing, subjects were given a standardized high-fat dinner meal. Subjects were administered study drug with 240 mL of noncarbonated water 30 minutes after the start of dinner.

Number of Subjects (planned and analyzed):

Planned: Approximately 42 subjects were planned to be enrolled to ensure that 36 subjects complete the study.

Analyzed: Forty-two (42) subjects were enrolled and randomized. Out of 42 subjects, 36 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Healthy men and women at least 18 to 55 years of age, inclusive; body mass index (BMI) between 18 and 30 kg/m², inclusive, and a body weight of not less than 50 kg. Systolic blood pressure between 90 and 140 mmHg and diastolic blood pressure no higher than 90 mmHg with a normal renal function (estimated Glomerular Filtration Rate [eGFR] ≥ 90 mL/min/1.73m² using the Modification of Diet in Renal Disease Study [MDRD] equation), were eligible for enrollment into the study.

Test Products 1 and 2, Dose and Mode of Administration, Batch No.: CANA/MET XR FDC were supplied as a 150/500 mg tablet which was taken orally with 240 mL of noncarbonated water.

- Test Product 1, manufactured at Gurabo, Batch no 13JG2581X; Expiry date: July 2014.
- Test Product 2, manufactured (b)(4) Batch no: a13LG3449X; Expiry date: September 2014.

Reference Therapy, Dose and Mode of Administration, Batch No.: Canagliflozin was supplied as a 300-mg tablet which was taken orally with 240 mL of noncarbonated water. Batch no: 13AG0462X; Expiry date: February 2016.

GLUMETZA[®] was supplied as a 500 mg tablet which was taken orally with 240 mL of noncarbonated water. Batch no: MTBT9431; Expiry date: October 2016.

Subjects randomly received three single-dose treatments, 1 dose during each Treatment Period as follows:

- Treatment A: 1 canagliflozin 300-mg tablet with 2 metformin XR 500-mg tablets (Reference)
- Treatment B: 2 CANA/MET XR FDC 150-mg/500-mg tablets (Test 1, metformin HCl granulate manufactured at Gurabo).

- Treatment C: 2 CANA/MET XR FDC 150-mg/500-mg tablets (Test 2, metformin HCl granulate manufactured (b) (4))

Duration of Treatment: Subjects received a single dose of 300 mg CANA and 1000 mg MET XR either as separate tablets or FDC tablets on Day 1 of the 3 treatment periods. The planned study duration was approximately 70 days.

Criteria for Evaluation:

Pharmacokinetics: Based on the individual plasma concentration-time data, using actual sampling times, the following key pharmacokinetic (PK) parameters of canagliflozin and metformin were calculated via noncompartmental methods for each treatment: C_{max} , t_{max} , AUC_{last} , AUC_{∞} and $t_{1/2,\lambda z}$.

Safety: Safety and tolerability were evaluated throughout the study and included the collection of adverse events (AEs) including hypoglycemia, subject's physical examination (including height [at screening] and body weight), evaluation of vital signs (blood pressure, pulse rate and body temperature), 12-lead electrocardiograms (ECGs) and laboratory tests (including hematology, serum chemistry, and urinalysis).

The total amount of blood to be withdrawn for clinical laboratory tests and PK evaluations was approximately 277 mL.

Statistical Methods: Sample size: The intrasubject coefficients of variation (CV) of AUCs (ie, AUC_{last} and AUC_{∞}) and C_{max} , respectively, were estimated to be no more than 22% for canagliflozin and no more than 16% for metformin XR for both the individual tablet and FDC tablet formulations. Assuming the intrasubject CV is the same as the maximum estimated CV of 22% for the PK endpoints of interest (AUCs and C_{max}), a sample size of 36 subjects who completed the study was considered sufficient to conclude bioequivalence of 2×150 mg/500 mg CANA/MET XR FDC tablets, respectively, compared with the individual components of canagliflozin (1×300-mg tablet) and metformin XR (2×500-mg tablets) at equal doses with an overall power of 80% (95% power for the individual components), when the between-treatment means differed by 5%.

Pharmacokinetic Analysis: Individual and mean canagliflozin and metformin plasma concentration-time profiles were plotted for each treatment. Plasma concentration data at each time point was summarized with mean, median, minimum, maximum, standard deviation (SD), and CV% for each treatment. All estimated pharmacokinetic parameters of canagliflozin and metformin were summarized with mean, median, geometric mean, minimum value, maximum value, SD, and CV% by treatment.

The statistical analysis was performed on log-transformed estimated pharmacokinetic parameters.

A mixed-effect model that includes treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect was used to estimate the least square means and intrasubject variability. Using these estimated least square means and intrasubject variability, 90% CIs for the ratio of geometric mean AUCs and C_{max} for the treatment ratios of B/A and C/A, respectively, were constructed and compared with the 80.00% to 125.00% bioequivalence limits. If the 90% CIs of the ratios fell within these limits, bioequivalence was concluded. If a subject vomited within 24 hours of dosing, the subject's data was excluded from the statistical analyses.

Safety: All subjects who were randomly assigned to treatment and received at least 1 dose of the study drug were included in the safety and tolerability analysis. Baseline values for all laboratory evaluations, vital signs, and 12-lead ECGs were defined as the last evaluation done before study drug administration of each period. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through study completion, including the washout interval.

RESULTS:

STUDY POPULATION: A total of 42 subjects were enrolled and randomly assigned to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA) with 7 subjects in each sequence. Out of the 42 enrolled subjects, 36 subjects completed the study. The reasons for withdrawal of the remaining 6 subjects were: adverse events (n=2), protocol violation (n=3) and withdrawal of consent (n=1). Median age of the subjects was 36.5 years (range: 20 to 52 years), the mean (SD) baseline body weight was 67.18 (8.89) kg, and the mean (SD) baseline BMI was 25.83 (2.35) kg/m². The majority of subjects enrolled were women compared to men (71% vs 29%). The majority of subjects were white (98%) and were Hispanic or Latino in ethnicity (90%).

There were no protocol deviations that impacted the subject's rights, safety, or well-being. There were 3 subjects with protocol violations which potentially could affect completeness, accuracy, and reliability of the study data; however, these subjects were appropriately withdrawn from the study that prevented the influence on study data. Two subjects were terminated at admission for Period 2 due to protocol violation (positive urine drug screen); one subject was terminated due to protocol violation (subject could not complete the standardized dinner in Period 2). All 42 subjects received at least 1 dose of study drug and were included in the safety analysis set.

PHARMACOKINETIC RESULTS:

Canagliflozin

As shown in the tables below, the canagliflozin component of the 150 mg/500 mg FDC tablet (Gurabo manufactured metformin HCl granulate) and the 150 mg/500 mg FDC tablet ^{(b) (4)} manufactured metformin HCl granulate), when administered as 2 tablets under fed conditions met the predefined BE criteria with respect to AUC_∞, AUC_{last}, and C_{max} relative to 1×300 mg canagliflozin + 2×500 mg metformin XR as the 90% CIs for the test-to-reference geometric mean ratios (GMRs) of these parameters were entirely contained within the prespecified BE limits of 80% to 125%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment B vs. Treatment A)

(Study 28431754DIA1063: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/500 mg]) (Treatment B, Test 1)	CANA (1 x 300 mg) + MET XR (2 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	36	2,949.05	2,944.25	100.16 (92.41 – 108.57)	21
AUC _{last} (ng.h/mL)	36	31,191.79	31,585.12	98.75 (95.96 – 101.63)	7
AUC _∞ (ng.h/mL)	35	31,995.65	32,336.63	98.95 (96.05 – 101.93)	7

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA (1 x 300 mg) + MET XR (2 x 500 mg)); Test = Treatment B (CANA/MET XR FDC tablet (2x[150 mg/500 mg], Gurabo- manufactured metformin HCl granulate)

CANA= Canagliflozin; CI= confidence interval; CV= coefficient of variance; FDC=fixed dose combination; MET=metformin; XR= extended release

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters (Treatment C vs. Treatment A)

(Study 28431754DIA1063: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/500 mg]) (Treatment C, Test 2)	CANA (1 x 300 mg) + MET XR (2 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	36	3,046.04	2,944.25	103.46 (95.44 – 112.15)	21
AUC _{last} (ng.h/mL)	36	30,913.42	31,585.12	97.87 (95.10 – 100.73)	7
AUC _∞ (ng.h/mL)	35	31,631.85	32,336.63	97.82 (94.95 – 100.77)	7

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA (1 x 300 mg) + MET XR (2 x 500 mg)); Test = Treatment C (CANA/MET XR FDC tablet (2x[150 mg/500 mg], ^{(b) (4)} manufactured metformin HCl granulate)

CANA= Canagliflozin; CI= confidence interval; CV= coefficient of variance; FDC=fixed dose combination; MET=metformin; XR= extended release

Metformin

As shown in the tables below, the metformin component of the 150 mg/500 mg FDC tablet (Gurabo manufactured metformin HCl granulate) and the 150 mg/500 mg FDC tablet ^{(b) (4)} manufactured metformin HCl granulate) when administered as 2 tablets under fed conditions, met the predefined BE criteria with respect to AUC_∞, AUC_{last} and C_{max} relative to 1x300 mg canagliflozin + 2x500 mg metformin XR as the 90% CIs for the test-to-reference GMRs of these parameters were entirely contained within the prespecified BE limits of 80% to 125%.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin Pharmacokinetic Parameters (Treatment B vs. Treatment A)

(Study 28431754DIA1063: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/500 mg]) (Treatment B, Test 1)	CANA (1 x 300 mg) + MET XR (2 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	36	1,032.72	1,028.52	100.41 (94.86 – 106.28)	15
AUC _{last} (ng.h/mL)	36	11,186.15	11,317.00	98.84 (92.91 – 105.16)	16
AUC _∞ (ng.h/mL)	34	11,186.32	11,327.38	98.75 (92.53 – 105.40)	16

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA (1 x 300 mg) + MET XR (2 x 500 mg)); Test = Treatment B (CANA/MET XR FDC tablet (2 x [150 mg/500 mg], Gurabo- manufactured metformin HCl granulate)

CANA= Canagliflozin; CI= confidence interval; CV= coefficient of variance; FDC=fixed dose combination; MET=metformin; XR= extended release

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Metformin Pharmacokinetic Parameters (Treatment C vs. Treatment A)

(Study 28431754DIA1063: Pharmacokinetic Statistical Analysis Set)

Parameter	N	Geometric Mean		Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
		CANA/MET XR FDC (2 x [150 mg/500 mg]) (Treatment C, Test 2)	CANA (1 x 300 mg) + MET XR (2 x 500 mg) (Treatment A, Reference)		
C _{max} (ng/mL)	36	1,017.73	1,028.52	98.95 (93.48 – 104.75)	15
AUC _{last} (ng.h/mL)	36	10,822.75	11,317.00	95.63 (89.88 – 101.75)	16
AUC _∞ (ng.h/mL)	34	10,844.13	11,327.38	95.73 (89.68 – 102.20)	16

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithms

Reference = Treatment A (CANA (1 x 300 mg) + MET XR (2 x 500 mg)); Test = Treatment C (CANA/MET XR FDC tablet (2 x [150 mg/500 mg], (b)(4) manufactured metformin HCl granulate)

CANA= Canagliflozin; CI= confidence interval; CV= coefficient of variance; FDC=fixed dose combination; MET=metformin; XR= extended release

SAFETY RESULTS:

Overall, 22/42 (52.4%) subjects reported at least 1 or more treatment-emergent adverse event (TEAEs). The most commonly reported TEAEs by system organ class were seen in gastrointestinal disorders (31.0% [13/42]) followed by nervous system disorders (16.7% [7/42]). The most commonly reported TEAEs (>3 subjects) by preferred term were nausea (n=7), headache (n=6), diarrhea (n=4), arthropod bite (n=4; verbatim: mosquito bite) and vomiting (n=4).

Overall, the incidence of TEAEs was generally low among all the 3 treatment groups. The incidence of TEAEs in subjects receiving 2 separate drug products (Treatment A) was comparable between treatment arms, numerically slightly higher versus fixed dose combination products ie, Treatment B and Treatment C (34.2% [13/38] vs. 23.7% [9/38] and 25.0% [10/40]).

The majority of the TEAEs (19/22) were mild in severity and majority of the TEAEs were judged by the investigator as “doubtfully” related to the study treatments. All the TEAEs resolved by the end of the study except 1 TEAE of “blood pressure increased” which started at follow up visit, was persistent, mild in severity and “doubtfully” related to Treatment B as experienced by a subject in Period 3. This subject had no previous history of hypertension and normal blood pressure at screening (130/81 mmHg), but at multiple occasions throughout the study, including baseline (Day -1) of all study periods, had modestly elevated systolic and/or diastolic blood pressure (Period 1: 155/89 mmHg, repeated 137/88 mmHg, Period 2: 140/100 mmHg, repeated 149/88 mmHg, Period 3: 146/88 mmHg all predose values). On Day 3 post dose in all the study periods, her blood pressure values were as follows: Period 1: 126/87 mmHg, Period 2: 141/84 mmHg, Period 3: 140/92 mmHg). At the end of the study visits (Day 11 Period 3) the subject returned with the blood pressure of 149/108 mmHg (repeats were 173/94 mmHg, 141/107 mmHg and 179/96 mmHg). The subject was advised by the principle investigator to follow up with the primary care physician for the treatment of elevated blood pressure, however the subject did not seek any medical care and the last measurement within the study was on Day 51, Period 3 when the blood pressure was 160/90 mmHg. During the study, no treatment dose modification was done for this TEAE and it did not resolve by the end of study.

There were no deaths or serious adverse events reported during the study. Two subjects discontinued the study treatment due to the AE of vomiting. Both the events were mild in severity and both resolved (one of the protocol-defined withdrawal criteria was vomiting within 24h of dosing). In 1 subject, vomiting was judged by the investigator as “very likely” related to Treatment B and in another subject it was judged as “probably” related to Treatment C.

One subject reported TEAEs as an increase in the 4 laboratory parameters of alanine aminotransferase (488 U/L [$>8 \times$ upper limit of normal {ULN}] on Day 6 Period 3), aspartate aminotransferase (up to 358 [$7 \times$ ULN]), lactate dehydrogenase, (451 U/L [$>1.5 \times$ ULN]) and gamma-glutamyltransferase (201 U/L) without increase in bilirubin level. The subject had no history of liver disorders or alcohol abuse at screening. The subject was asymptomatic, with no findings in physical examination and denied any concomitant medication (including herbal medicine or paracetamol) or alcohol use throughout the study. His serology for hepatitis A, B and C were negative at screening. The hepatitis B soluble antibody and the core antibody were both nonreactive. The hepatitis C virus RNA was not detected. The cytomegalovirus (CMV) and Epstein-Barr virus (EBV) IgM antibodies were within normal range, while the IgG results for both tests were elevated, indicating prior infection. The elevated liver function tests returned to values close to normal by Day 27 Period 3. They were considered by the investigator as mild in severity and possibly related to Treatment C.

There were no mean changes in the hematology and biochemistry laboratory parameters which were considered clinically significant. Moderate mean changes, i.e., increases or decreases from baseline (Period 1 Day -1) to Period 3 Day 3 or at the end of the study in certain laboratory analytes such as creatinine, creatine kinase, serum urate and eGFR were observed. However, all these changes were transient and within prespecified normal ranges.

Other than a small decrease in systolic blood pressure, as seen in prior canagliflozin studies, there were no apparent or consistent treatment-related changes from baseline in mean vital sign measurements (pulse rate, blood pressure and body temperature), ECG parameters, or physical examinations.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

- The 2×150 mg/500 mg CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2×150 mg/500 mg CANA/MET XR FDC tablets containing the ^{(b)(4)} manufactured metformin HCl granulate were each bioequivalent to the coadministered 1× 300 mg canagliflozin and 2×500 mg metformin XR tablets in the fed state with respect to C_{max} and AUCs for both canagliflozin and metformin.
- The 2×150 mg/500 mg CANA/MET XR FDC tablets containing Gurabo manufactured metformin HCl granulate and the 2×150 mg/500 mg CANA/MET XR FDC tablets containing the ^{(b)(4)} manufactured metformin HCl granulate were safe and well tolerated with no new, unexpected, or unusual safety signals.

4.3.5. DIA1042 – MULTIPLE-DOSE PK STUDY

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	To be determined
<u>Name of Active Ingredients</u>	JNJ-28431754 ([Canagliflozin] + JNJ-1158196 [Metformin XR]))

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 13 October 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1042, Phase 1

Title of Study: An Open-Label Study to Evaluate the Multiple Dose Pharmacokinetics of Canagliflozin (JNJ-28431754) and Metformin Following Once-Daily Administration of 2 Canagliflozin/Metformin XR (150/1,000-mg) Fixed Dose Combination Tablets in Healthy Subjects.

NCT No.: NCT02039245

Clinical Registry No.: CR103255

Principal Investigator(s): Hosein A. Fareeda, MD

Study Center(s): Celerion, Inc., 1930 Heck Avenue Building 2, Neptune, NJ 07753 USA

Publication (Reference): None

Study Period: 23 January 2014 to 28 February 2014

Phase of Development: 1

Objectives: The primary objective of this study was to evaluate the multiple dose pharmacokinetics (PK) of 2 canagliflozin (CANA)/metformin (MET) extended release (XR) fixed dose combination (FDC) (CANA/MET XR FDC) tablets (150 mg/1,000 mg each) following once-daily oral doses in healthy subjects.

The secondary objectives was to assess safety and tolerability.

Methodology: This was an open-label, multiple-dose, single-center, PK study conducted in 12 healthy adult men and women. The study consisted of 3 phases: a Screening Phase of approximately 3 weeks (Days -22 to -2), an Open-Label Treatment Phase of 11 days (Days -1 through 10), with daily dosing from Day 1 to Day 7 and sample collection up to Day 10, and a Follow-up Phase occurred after 7 to 10 days after the last study related procedure on Day 10.

On the evening of Day 1, thirty minutes before dosing, subjects were given a standardized dinner meal, and they had to consume the entire dinner meal within 30 minutes or less. Subjects received a single oral dose of 2 XR FDC tablets with 240 mL of noncarbonated water (150 mg/1,000 mg CANA/MET XR tablet) 30 minutes after the start of the dinner meal. Subjects were restricted from liquids from 1 hour before the dinner meal to 1 hour after dosing, with the exception of any liquids consumed with dinner and

dosing. Subjects continued to receive once-daily oral doses of 2 CANA/MET XR FDC tablets (150 mg/1,000 mg CANA/MET XR/tablet) in the evening, immediately following the completion of the dinner meal (Day 2 to Day 6) or 30 minutes after the start of a standardized dinner meal (Day 7) at approximately the same time each evening.

On Days 1 and 7, subjects fasted from the end of lunch until the start of dinner (a period of at least 6.5 hours). The standardized meals and snacks on Days 1, 2, 7 and 8 were identical in terms of content and amount for all subjects. Subjects were asked to complete the snack on Days 1 and 7 and the breakfast and lunch meals on Days 2 and 8 in their entirety.

On Day 7, subjects received their final dose of study agent and remained at the study center for collection of PK samples and safety assessments for up to 72 hours (Day 10). Subjects were discharged from the study center on Day 10 after all PK sample collections were completed. Subjects returned to the study center within 7 to 10 days after the last study related procedure on Day 10.

Number of Subjects (planned and analyzed):

Planned: Approximately 12 healthy adult men or women who met the study inclusion and exclusion criteria were planned to be enrolled in the study.

Analyzed: A total of 12 healthy adult men were enrolled in the study; 2 subjects were prematurely discontinued from the study. All subjects were included in the safety and tolerability analysis. The 2 subjects who did not complete the study were included in the PK analysis set for Day 1; however, no PK data were reported for Day 7.

Diagnosis and Main Criteria for Inclusion: Subjects were men or women at least 18 (or the legal age of consent in the jurisdiction in which the study was to take place) to 55 years of age, inclusive; body mass index (BMI) between 18 and 30 kg/m², inclusive, and a body weight of not less than 50 kg.

Test Product, Dose and Mode of Administration, Batch No.: CANA/MET XR FDC, tablet, 2x150 mg/1,000 mg, administered oral (Batch number 13JG2578X with expiration date July 2014).

Duration of Treatment: The study consisted of 3 phases: a screening phase (Days -22 to -2), treatment phase (Days -1 to 10), including dosing from Day 1 to Day 7, and up to 10-day follow-up period. The entire duration of the study for each subject was approximately 42 days.

Criteria for Evaluation:

Pharmacokinetics

Based on the individual concentration-time data, given actual sampling times, the following plasma PK parameters of CANA and MET were determined as appropriate: Day 1: C_{max} , t_{max} , and $AUC_{\tau,SD}$; Day 7: $C_{max,ss}$, C_{trough} , $C_{min,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, Acc Ratio, $t_{1/2}$.

Safety

Safety and tolerability were evaluated throughout the study via repeated physical examinations, vital sign measurements, routine clinical safety laboratory assessments (chemistry, hematology, and urinalysis), fingerstick glucose measurements and electrocardiogram (ECGs), at specified timepoints, and assessment of adverse events (AEs).

Statistical Methods:

Sample Size Determination

Based on a previous study (Clinical Study Report 28431754DIA1033), the inter-subject coefficient of variation (CV) of both AUC_{∞} and C_{max} were estimated to be no more than 32% and 26% for CANA and MET, respectively, after a single oral dose of CANA/MET XR FDC. Assuming that the inter-subject CV for multiple dose CANA/MET XR FDC was similar to that for single dose, with an inter-subject CV of 32%, a sample size of 8 subjects would be sufficient to estimate the geometric mean. Pharmacokinetic parameters of CANA and MET (ie, AUC_{τ} and C_{max}) following multiple once daily oral doses of 2x150 mg/1,000 mg CANA/MET XR FDC was expected to be within 76.5% and 130.7% of their true values with 95% confidence.

Twelve subjects were enrolled to allow for dropouts. Additional subjects were to be enrolled if the number of subjects who complete the study drops below 8.

Pharmacokinetics

Individual and mean CANA and MET plasma concentration-time profiles on Day 1 (up to 24 hours postdose) and Day 7 (up to 72 hours postdose) were plotted by treatment. Plasma concentration data collected on Day 1 (up to 24 hours postdose), Days 3 through 6 (predose), and Day 7 (up to 72 hours postdose) were summarized with mean, median, minimum, maximum, standard deviation (SD), and CV (%) by treatment. All PK parameters of CANA and MET were summarized with mean, median, geometric mean, minimum value, maximum value, SD, and CV (%) by treatment.

Safety

All subjects who received at least 1 dose of study agent were included in the safety and tolerability analysis. Baseline values (for all laboratory and safety evaluations, vital signs) were defined as the value at the last evaluation done before the first dose. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, and vital signs measurements beginning with the Screening Phase through the final follow-up visit.

RESULTS:

STUDY POPULATION:

A total of 12 healthy men between 18 and 55 years of age were enrolled and received at least 1 dose of the study agent. Of the 12 subjects, 10 subjects completed the study, while the remaining 2 subjects were prematurely discontinued from the study during the treatment phase. Both subjects discontinued early as they did not consume the entire standardized meal on Day 7 and did not receive the last dose (for 1 subject the reason for discontinuation was considered to be a protocol violation, for another subject it was reported as “other”; however, the reason for discontinuation should have been reported as “protocol violation” as for other discontinued subject).

The median age was 30 years (range: 25 to 43 years), mean (SD) BMI was 25.3 kg/m² (2.5 kg/m²), mean (SD) body weight was 80.4 kg (9 kg), and mean (SD) baseline estimated Glomerular Filtration Rate was 106.7 mL/min/1.73m² (9.8 mL/min/1.73m²). The majority of the subjects were black or African-American (75%).

PHARMACOKINETIC RESULTS: Following both single- (Day 1) and multiple-dose (Day 2 to Day 7) once-daily administration of 2x150 mg/1,000 mg CANA/MET XR FDC tablets with an evening meal, plasma CANA and MET concentrations increased. Mean plasma CANA and MET concentration-time profiles on Day 1 and Day 7 had a similar shape, with higher CANA and MET concentrations achieved on Day 7.

Mean C_{max} and AUC_{τ} values for CANA increased on Day 7 (steady-state) compared to Day 1 (single dose). The accumulation ratios of C_{max} and AUC_{τ} on Day 7 to Day 1 were 1.33 and 1.36, respectively. Median t_{max} was similar on Day 7 and Day 1 and the mean $t_{1/2}$ was approximately 18 hours on Day 7.

Arithmetic Mean (SD) Plasma Canagliflozin Pharmacokinetic Parameters

PK Parameter	CANA/MET XR FDC (2 x [150 mg/1,000 mg]) (Day 1) n=12	CANA/MET XR FDC (2 x [150 mg/1,000 mg]) (Day 7) n=10
C_{max} (ng/mL)	2,318 (565)	3,078 (464)
$C_{min,ss}$ (ng/mL)	NA	416 (109)
t_{max} (h) ^a	2.50 (1.50 – 8.00)	1.75 (1.50 – 4.00)
$AUC_{\tau,sd}$ (ng.h/mL)	19,505 (2,598)	NA
$AUC_{\tau,ss}$ (ng.h/mL)	NA	26,320 (3,672)
$t_{1/2}$ (h)	NA	17.6 (5.52)
Acc Ratio ^b	NA	1.36 (0.143)

^a Median (range)

^b Based on AUC

Key: CANA=canagliflozin; FDC=fixed dose combination; MET=metformin; NA = Not applicable;
PK=pharmacokinetic; SD=standard deviation; XR=extended release

Mean C_{max} and AUC_{τ} values for MET were slightly higher on Day 7 (steady-state) compared to Day 1 (single dose). The accumulation ratios of C_{max} and AUC_{τ} on Day 7 to Day 1 were 1.10 and 1.18, respectively. Median t_{max} was similar on Day 7 and Day 1 and the mean $t_{1/2}$ was approximately 7 hours on Day 7.

Arithmetic Mean (SD) Plasma Metformin Pharmacokinetic Parameters

PK Parameter	CANA/MET XR FDC (2 x [150 mg/1,000 mg]) (Day 1) n=12	CANA/MET XR FDC (2 x [150 mg/1,000 mg]) (Day 7) n=10
C_{max} (ng/mL)	1,434 (285)	1,581 (251)
$C_{min,ss}$ (ng/mL)	NA	183 (54.8)
t_{max} (h) ^a	10.0 (4.00 – 10.0)	8.00 (4.00 – 12.0)
$AUC_{\tau,sd}$ (ng.h/mL)	16,604 (3,282)	NA
$AUC_{\tau,ss}$ (ng.h/mL)	NA	19,386 (3,454)
$t_{1/2}$ (h)	NA	7.14 (0.730)
Acc Ratio ^b	NA	1.18 (0.231)

^a Median (range)

^b Based on AUC

Key: CANA=canagliflozin; FDC=fixed dose combination; MET=metformin; NA = Not applicable;
PK=pharmacokinetic; SD=standard deviation; XR=extended release

SAFETY RESULTS: There were no deaths, serious AEs and no AEs leading to discontinuation reported in the study. Three of the 12 subjects reported at least 1 treatment-emergent adverse event (TEAE). The most commonly reported TEAEs by system organ class (SOC) were in the gastrointestinal disorders SOC (3 [25%] of 12 subjects). TEAEs reported by PT were abdominal distension (2 subjects), diarrhea, nausea, hypoglycemia, and lethargy (1 subject each). All of the reported AEs were considered as mild in severity except for the hypoglycemia event which was considered as moderate. The AEs of distension, diarrhea, and hypoglycemia were considered as very likely related to the study agent. All AEs were reported as resolved at the end of the study.

No clinically meaningful abnormalities in laboratory tests, vital signs measurements, physical examinations, and ECGs recordings were observed during the study.

STUDY LIMITATIONS: This study did not include placebo group, as the main objective of the study was PK which is an objective parameter.

CONCLUSION(S):

- There was no evidence of dose dumping for the CANA/MET XR FDC formulation.
- There were increases in CANA of 33% and 36% for C_{max} and AUC, respectively, and increases in MET of 10% and 18% for C_{max} and AUC, respectively, after 7 days of once-daily dosing.
- Steady-state for CANA was reached by the 6th dose and for MET by the 3rd dose.
- The highest therapeutic dose of CANA/MET XR FDC tablet (2x150 mg/1,000 mg) was generally well tolerated in healthy subjects. No unexpected safety concerns were noted during the study.

APPEARS THIS WAY ON ORIGINAL

4.3.6. DIA1064 – FOOD EFFECT STUDY

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	To be determined
<u>Name of Active Ingredient(s)</u>	JNJ-28431754 (Canagliflozin + JNJ-1158196 [Metformin XR])

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 13 October 2014
Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1064

Title of Study: A Single-Dose, Open-Label, Randomized, 2-Period Crossover Study to Assess the Effect of Food Coadministration on the Pharmacokinetics of a Fixed Dose Combination Tablet of Canagliflozin (JNJ-28431754) and Metformin Extended Release in Healthy Subjects

NCT No.: NCT02039258

Clinical Registry No.: CR103259

Coordinating Principal Investigator: Barbara J. Cook, MD, Celerion Inc., Lincoln, NE, United States

Study Center: Celerion Inc., 621 Rose Street, Lincoln, NE 68502, United States

Publication (Reference): None

Study Period: 24 January 2014 to 20 March 2014; Database lock date: 24 April 2014

Phase of Development: 1

Objectives: The primary objective was to assess the effect of coadministration of a high-fat meal on the oral bioavailability of fixed dose combination (FDC) tablet of canagliflozin (CANA) and extended-release metformin (MET XR), containing 150 mg CANA and 1,000 mg MET XR, respectively in healthy subjects.

The secondary objectives were to assess the safety and tolerability of a 150 mg/1,000 mg CANA/MET XR FDC tablet under fed and fasted conditions.

Methodology: This was a randomized, open-label, single-dose, 2-period, 2-sequence, crossover study to evaluate the relative bioavailability of CANA and MET after oral administration of a single 150 mg/1,000 mg CANA/MET XR FDC tablet to healthy subjects under fasted conditions and after coadministration with food. Subjects were screened within 21 days of Day -1 of Period 1 of the Open-label Treatment Phase (Days -22 to -2) and all eligible subjects were admitted to the study center on Day -1 of Period 1.

All the subjects received a single 150 mg/1,000 mg CANA/MET XR FDC tablet under fasted (Treatment A) or fed (Treatment B) conditions on Day 1 of each Treatment Period. Subjects were

randomly assigned to 1 of the 2 treatment sequences ie, AB or BA, on Day 1 of Period 1 prior to study drug administration. There was a 10- to 14-day washout period between Day 1 of each Treatment Period.

For Treatment A (fasted state), the study drug was administered in the morning with 240 mL of noncarbonated water following an overnight fast of at least 10 hours. Water was allowed as desired except for 1 hour prior to and after CANA/MET XR FDC tablet administration.

For Treatment B (fed condition), subjects were given a standardized high-fat breakfast consisting of 2 strips of fried bacon, 2 eggs fried in butter, 4 ounces (120 gram) hash brown potatoes fried in butter, 2 buttered pieces of white toast and 240 mL whole milk following an overnight fast of at least 10 hours. Subjects were asked to consume the entire meal in 30 minutes or less. The 150 mg/1,000 mg CANA/MET XR FDC tablet was administered 30 minutes after the start of the meal with 240 mL of noncarbonated water. Water was allowed as desired except for 1 hour before the breakfast meal to 1 hour after CANA/MET XR FDC tablet administration.

For both the treatments, subjects remained upright (standing or sitting) for the first 4 hours after dosing and no food was allowed for at least 4 hours after dosing.

Number of Subjects (planned and analyzed): Planned: Twenty-four healthy men and women enrolled to ensure at least 20 subjects completed the study. Analyzed: All 24 subjects (16 men and 8 women) were randomized and completed the safety and pharmacokinetic (PK) analysis.

Diagnosis and Main Criteria for Inclusion: Healthy men or women between 18 and 55 years of age (inclusive), who had a body mass index (BMI) between 18 and 30 kg/m² (inclusive) and body weight of not less than 50 kg with normal renal function (estimated glomerular filtration rate ≥ 90 mL/min/1.73m²) using Modification of Diet in Renal Disease Study equation), were eligible for enrollment into the study.

Test Product, Dose and Mode of Administration, Batch No.: CANA/MET XR FDC, 1 x 150 mg/1,000 mg tablet, was taken orally with 240 mL of noncarbonated water under fed (high-fat meal) conditions (Treatment B). Batch no: 13JG2578X; Expiry date: July 2014.

Reference Therapy, Dose and Mode of Administration, Batch No.: CANA/MET XR FDC, 1 x 150 mg/1,000 mg tablet, was taken orally with 240 mL of noncarbonated water under fasted conditions (Treatment A). Batch no: 13JG2578X; Expiry date: July 2014.

Duration of Treatment: The study consisted of 3 phases: a Screening Phase (up to 21 days), a Treatment Period up to 19 days (including a washout period of up to 14 days between Day 1 of each treatment period), and up to 10-day Follow-up Period. The entire duration of the study for each subject was approximately 51 days.

Criteria for Evaluation:

Pharmacokinetic: Based on the individual plasma concentration-time data, using actual sampling times, the following PK parameters were determined via noncompartmental methods for CANA and MET for each treatment: C_{max} , t_{max} , AUC_{last} , AUC_{∞} , and $t_{1/2,\lambda}$.

Safety: Safety and tolerability were evaluated throughout the study and included the collection of adverse events (AEs) including hypoglycemia, subject's physical examination (including height and body weight), evaluation of vital signs (blood pressures, pulse rates and body temperature), 12-lead electrocardiograms (ECGs) and safety laboratory tests (including hematology, chemistry and urinalysis).

The total amount of blood to be withdrawn for clinical laboratory tests and PK evaluations was approximately 206 mL.

Statistical Methods:

Sample Size Determination: Based on study 28431754DIA1033, a relative bioavailability study of metformin XR FDC with food, the intrasubject coefficient of variation (CV) of both AUC_{∞} and $C_{\max}$ was estimated to be no more than 22% for CANA and no more than 16% for MET. Using an estimated 22% intrasubject CV for both AUC_{∞} and $C_{\max}$ for CANA, a sample size of 20 subjects who completed the study was considered sufficient for the ratio of geometric mean AUC_{∞} and $C_{\max}$ of CANA with food to without food to fall within 89% to 113% of the true value with 90% confidence. Using an estimated intrasubject CV of 16% for both AUC_{∞} and $C_{\max}$ of MET, a sample size of 20 subjects who completed the study was considered sufficient for the ratio of geometric mean AUC_{∞} and $C_{\max}$ of MET with food to without food to fall within 92% to 109% of the true value with 90% confidence.

Pharmacokinetic Assessments: Individual and mean CANA and MET plasma concentration-time profiles were plotted for each treatment (fed and fasted). Plasma concentration data at each timepoint were summarized with mean, median, minimum, maximum, standard deviation (SD), and CV (%) for each treatment. All PK parameters of CANA and MET were summarized with mean, median, geometric mean, minimum value, maximum value, SD, and CV (%) by treatment.

Statistical analysis was performed on a log-transformed data from subjects who completed the study. A mixed-effects analysis of variance model that included the treatment, period, and treatment sequence as fixed effects, and subjects as random effect was used to estimate the least squares means and intrasubject variance. Using these estimated least squares means and intrasubject variance, the point estimate and 90% confidence intervals (CI) for the difference in means on a log scale between Treatment B (test treatment; under fed state) and Treatment A (reference treatment; under fasting state) was constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUCs and $C_{\max}$ of the test (fed state) to reference (fasting state) treatments.

Safety: All subjects who were randomly assigned to a treatment sequence and received 1 dose of the study drug were included in the safety and tolerability analysis. Baseline evaluations for all laboratory evaluations and vital signs were defined as the last evaluation done before study drug administration in each period. Baseline for physical examination results was the screening evaluation. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, and vital signs measurements from the screening phase through study completion, including the washout interval.

RESULTS:

STUDY POPULATION:

A total of 24 subjects were enrolled and randomly assigned to treatment sequences (12 subjects each, in Sequences AB and BA). All subjects completed the study. The median age of the subjects was 26 years (range: 19 to 53 years). The mean (SD) baseline body weight was 74.2 (10.0) kg and body mass index was 25.0 (2.7) kg/m². Majority of the subjects were white (63%) and Black or African American (25%) with more men (67%) than women (33.3%) enrolled in this study.

There were no protocol deviations in this study that impacted the subject's rights, safety, or well-being or the completeness, accuracy, and reliability of the study data.

PHARMACOKINETIC RESULTS:

Canagliflozin

Mean plasma CANA concentrations after single-dose administration of 1 x 150 /1,000 mg CANA/MET XR FDC tablet under fed and fasting conditions had a similar shape and peaked at a median t_{max} of approximately 2.0 hours.

The table below shows the geometric mean ratio (fed to fasted) for C_{max} was 88.17% and the 90% confidence interval (CI) was 79.53% to 97.75%. For AUC_{∞} , the geometric mean ratio (fed to fasted) was 104.49% and the 90% CI was 101.20% to 107.89%.

Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Canagliflozin Pharmacokinetic Parameters Following Administration of 1 x 150/1,000 mg CANA/MET XR FDC Tablet With and Without Food

Parameter	Geometric Mean		Geometric Mean Ratio (%) (90% CI)
	Canagliflozin Treatment B Fed (Test) N=24	Canagliflozin Treatment A Fasted (Ref) N=24	
C_{max} (ng/mL)	1,241.78	1,408.34	88.17 (79.53; 97.75)
AUC_{last} (ng.h/mL)	12,455.18	11,956.54	104.17 (100.81; 107.64)
AUC_{∞} (ng.h/mL)	12,782.49	12,232.88	104.49 (101.20; 107.89)

CANA = Canagliflozin; FDC = fixed dose combination; MET = Metformin; XR = extended release

Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithms

Ref = Treatment A (CANA/MET XR FDC tablet, 1 x 150 mg/1,000 mg) administered under fasted conditions

Test = Treatment B (CANA/MET XR FDC tablet, 1 x 150 mg/1,000 mg) administered under fed conditions

Metformin

Plasma MET concentrations peaked at a median t_{max} of 4.0 hours and 6.0 hours following administration of the FDC tablet without food and with food, respectively. Mean elimination $t_{1/2}$ of MET was 5.45 hours and 10.9 hours under fed and fasting conditions, respectively.

The table below shows the geometric mean ratio (fed to fasted) for C_{max} was 113.03% and the 90% CI was 98.64% to 129.51%. For AUC_{∞} , the geometric mean ratio (fed to fasted) was 160.61% and the 90% CI was 143.20% to 180.13%.

Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Metformin Pharmacokinetic Parameters Following Administration of 1 x 150/1,000 mg CANA/MET XR FDC Tablet With and Without Food

Parameter	Geometric Mean		Geometric Mean Ratio (%) (90% CI)
	Metformin Treatment B Fed (Test) N=24	Metformin Treatment A Fasted (Ref) N=24	
C _{max} (ng/mL)	917.15	811.45	113.03 (98.64; 129.51)
AUC _{last} (ng.h/mL)	10,607.86	6,181.44	171.61 (152.83; 192.70)
AUC _∞ (ng.h/mL) ^a	10,927.94	6,804.15	160.61 (143.20; 180.13)

^a n=20; Subjects 107, 108, and 123 (MET; Treatment A) and Subject 115 (MET; Treatment B) were excluded from the arithmetic mean and statistical analyses of AUC_∞ since the regression fit for the determination of the terminal phase was unacceptable (r²adj. <0.90)

CANA = Canagliflozin, CI = confidence interval, FDC = fixed dose combination, MET = Metformin, XR = extended release
 Note: Analysis was done on log-transformed data and the results were back-transformed using anti-logarithm
 Ref = Treatment A (CANA/MET XR FDC tablet, 1 x 150 mg/1,000 mg) administered under fasted conditions
 Test = Treatment B (CANA/MET XR FDC tablet, 1 x 150 mg/1,000 mg) administered under fed conditions

SAFETY RESULTS:

There were no deaths, serious adverse events, events leading to discontinuation or persistent events reported in this study. Overall, 15/24 (62.5%) subjects had 1 or more treatment-emergent adverse events (TEAEs). The most commonly reported TEAEs as per system organ class were seen in gastrointestinal disorders (33.3%; 8/24 subjects) and by preferred term were diarrhea (n=4), postural dizziness (n=3), abdominal pain (n=2), nausea (n=2), and headache (n=2).

Overall, the incidence of subjects with 1 or more TEAEs was comparable following the administration of CANA+MET in the fed state and fasted state (42% vs. 33.3%). The incidence of TEAEs by preferred term was low in both fed and fasted groups with no TEAE reported in more than 2 subjects in either of the groups. There was no apparent relationship between the study drug dosing conditions (ie, fed vs. fasted state) and the incidence, type, or duration of specific TEAEs. All the reported TEAEs were of mild severity with the majority of the events judged by the investigator as either “possibly” or “probably” related to the study drug.

Overall, there were no treatment-related changes from baseline at various timepoints of assessments in any of the clinical laboratory analytes (ie, hematology, chemistry, and urinalysis). There were no apparent or consistent treatment-related changes from baseline in mean vital sign measurements (systolic and diastolic blood pressure, pulse rate, and body temperature), ECG parameters, or physical examinations.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- Administration of a high-fat meal with a single oral 150-mg/1,000-mg CANA/MET XR FDC tablet did not have a clinically meaningful effect on canagliflozin pharmacokinetics.
- Administration of a high-fat meal with a single oral 150-mg/1,000-mg CANA/MET XR FDC tablet increased metformin AUC by 60% to 72%, consistent with the reported food effect for Glumetza®.
- Overall, a single oral 150-mg/1,000-mg CANA/MET XR FDC tablet was well tolerated in both fasting and fed conditions in healthy subjects.

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/s/

RENU SINGH
08/16/2016

MANOJ KHURANA
08/16/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	205879	SDN	0000
Applicant	Janssen Research & Development, LLC	Submission Date	11/20/2015
Generic Name	Canagliflozin/Metformin XR FDC	Brand Name	INVOKAMET XR®
Drug Class	Sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination		
Indication	Type 2 diabetes mellitus		
Dosage Regimen	Once daily		
Dosage Form	Tablet	Route of Administration	Oral
OCP Division	DCP 2	OND Division	DMEP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Renu Singh, PhD	Manoj Khurana, PhD	
Pharmacometrics			
Genomics			
Review Classification	☒ Standard ☐ Priority ☐ Expedited		
Filing Date	1/19/2016	74-Day Letter Date	2/2/2016
Review Due Date	8/16/2016	PDUFA Goal Date	9/20/2016
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
☒ Yes			
☐ No			
If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
☐ Yes			
☒ No			
If yes list comment(s)			
Is there a need for clinical trial(s) inspection?			
☒ Yes			
☐ No			
If yes explain: OSIS consult request sent for Pivotal BE study DIA1063			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies		☒ Yes ☐ No	Clinical Pharmacology Summary
Bioanalytical and Analytical Methods		☒ Yes ☐ No	Labeling
			☒ Yes ☐ No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☒ Drug-Drug Interaction		DIA1063 (Module 3.2.P.2.2.3)- Study to evaluate the alcohol-induced dose	

dumping for the modified release layer

In Vivo Studies					
Biopharmaceutics					
☐ Absolute Bioavailability					
☐ Relative Bioavailability					
☒ Bioequivalence	5	DIA1041, DIA1044, DIA1062, DIA1063 (Module 5.3.1.2) (pivotal BE effect study) DIA1033 (Module 5.3.1.2) (pilot study)			
☒ Food Effect	1	DIA1064 (Module 5.3.1.2) (pivotal food effect study)			
☐ Other					
Human Pharmacokinetics					
Healthy Subjects	☒ Single Dose	6	DIA1041, DIA1044, DIA1062, DIA1063 (Module 5.3.1.2), DIA1064 (Module 5.3.1.2), DIA1033 (Module 5.3.1.2) (pilot study)		
	☒ Multiple Dose	1	DIA1042 (Module 5.3.3.1)		
Patients	☐ Single Dose				
	☐ Multiple Dose				
☐ Mass Balance Study					
☐ Other (e.g. dose proportionality)					
Intrinsic Factors					
☐ Race					
☐ Sex					
☐ Geriatrics					
☐ Pediatrics					
☐ Hepatic Impairment					
☐ Renal Impairment					
☐ Genetics					
Extrinsic Factors					
☐ Effects on Primary Drug					
☐ Effects of Primary Drug					
Pharmacodynamics					
☐ Healthy Subjects					
☐ Patients					
Pharmacokinetics/Pharmacodynamics					
☐ Healthy Subjects					
☐ Patients					
☐ QT					
Pharmacometrics					
☐ Population Pharmacokinetics					
☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies	8	In Vitro	1	In Vivo	7
Total Number of Studies to be Reviewed	7				6

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☒ Yes ☐ No ☐ N/A	The sponsor claims that tablets of the proposed commercial formulations (film-coated), manufactured at commercial scale, at the commercial site JOLLC, Gurabo, and using final manufacturing equipment were used in the pivotal BE studies.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐ Yes ☐ No ☒ N/A	Cross- reference to NDA 204042
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☒ Yes ☐ No ☐ N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐ Yes ☐ No ☒ N/A	Comparative study information provided for XR and individual components of the combination in the 505(b)(1) application.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☒ Yes ☐ No ☐ N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐ Yes ☐ No ☒ N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☒ Yes ☐ No ☐ N/A	No PD data provided. For PD data Cross-reference to NDA 204042.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☒ Yes ☐ No ☐ N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☒ Yes ☐ No ☐ N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input	☒ Yes ☐ No ☐ N/A	The sponsor conducted study DIA1042 (multi-dose PK) and in-vitro studies to assess dose-dumping

files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		as suggested by FDA at the EOP2 meeting.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☒ Yes ☐ No ☐ N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐ Yes ☐ No ☒ N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☒ Yes ☐ No ☐ N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐ Yes ☐ No ☒ N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐ Yes ☐ No ☒ N/A	Cross- reference to NDA 204042
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐ Yes ☐ No ☒ N/A	Cross- reference to NDA 204042
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐ Yes ☐ No ☒ N/A	Request for a waiver of studies in children ages 0 – 10 years, and a deferral request for older children and adolescents ≥ 10 to ≤ 18 years of age.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☒ Yes ☐ No ☐ N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐ Yes ☐ No ☒ N/A	

NDA 205879 Filing Meeting

Canagliflozin and Metformin hydrochloride
extended release tablets

Sponsor: Janssen Pharmaceuticals, Inc

Submitted: 20th Nov 2015

Filing meeting: 11th Jan 2016

OCP Review Team:

Clin Pharm Reviewer: Renu Singh, PhD

Clin Pharm Team Leader: Manoj Khurana, PhD

Overview

- **Type of Submission: 505(b)(1)**
 - Canagliflozin submitted under NDA 204042 and approved at 100 or 300 mg per day dose in 2013.
 - Cana + Met IR was approved under NDA 204353 in 2014.
- **Proposed Indications:**
 - CANA/MET XR FDC is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate.
- **Formulation and Strength:**

<u>Cana /Met XR FDC (qd dosing with the morning meal)</u>	<u>Approved IR FDC: Cana /Met IR FDC (bid dosing with meals)</u>
2 tablets 50 mg/500 mg qd	1 tablet 50 mg/500 mg bid
2 tablets 50 mg/1000 mg qd	1 tablet 50 mg/1000 mg bid
2 tablets 150 mg/500 mg qd	1 tablet 150 mg/500 mg bid
2 tablets 150 mg/1000 mg qd	1 tablet 150 mg/1000 mg bid

Proposed Dose:

Individualize the starting dose of once-daily INVOKAMET XR (CANA/MET XR FDC) based on the effectiveness and tolerability of the patient's current regimen:

(b) (4)

- In patients already treated with canagliflozin and metformin, switch to two INVOKAMET XR tablets containing the same daily dose of canagliflozin and the same, or nearest appropriate, daily dose of metformin
- Take two INVOKAMET XR tablets once daily with the morning meal, with gradual dose escalation, if needed, to reduce the gastrointestinal side effects due to metformin.
- INVOKAMET XR must be swallowed whole and never crushed, cut, or chewed.
- Maintain the same total daily dose of canagliflozin and metformin when changing between INVOKAMET and INVOKAMET XR.

Two sources of metformin HCl granulate were tested in the pivotal BE studies

- Metformin HCl granulate without the release-controlling polymers for the CANA/MET XR FDC tablet were manufactured in 2 facilities:
 - JOLLC, Gurabo
- (b) (4)
- The release-controlling polymers were added in JOLLC, Gurabo and compression of the bilayer tablets also occurred in JOLLC, Gurabo.

Overview of Clin. Pharm. Program

Study	Objective towards TBM CANA/MET XR FDC
DIA1041	BE for 50/500 XR FDC to the individual components of canagliflozin and metformin XR
DIA1062	BE for 50/1000 XR FDC to the individual components of canagliflozin and metformin XR
DIA1044	BE for 150/500 XR FDC to the individual components of canagliflozin and metformin XR
DIA1063	BE for 150/1000 XR FDC to the individual components of canagliflozin and metformin XR
DIA1042	7-day multiple QD PK study of the 150/1000 mg CANA/MET XR FDC
DIA1064	Food effect study following single-dose of 150/1000 mg CANA/MET XR FDC
DIA1033	Pilot BE Study

Data from the Pivotal Phase 3 initial combination therapy study (DIA3011) and from the extension phase of Phase 3 studies DIA3009 and DIA3010 (up to Week 104) were also submitted.

Sponsor claims adequate bridging of CANA and MET exposure from FDC Tablet in pivotal BE studies

DIA1041: 50/500-mg XR FDC tablets (administered as 2 tablets) to the individual tablets (1 × 100 mg INVOKANA and 2 × 500 mg extended-release Glumetza under fed conditions

Parameter	N	CANA/MET XR FDC (2 x [50/500 mg]) (Treatment B, Test 1)	CANA (1 x 100 mg) + MET XR (2 x 500 mg) (Treatment A, Reference)	Geometric Mean Ratio % (90% CI)
		<u>Canagliflozin</u>		
C _{max} , ng/mL	41	924.84	938.84	98.51 (91.46 – 106.10)
AUC _{0-∞} , ng.h/mL	40	9,490.94	9,402.40	100.94 (98.88 – 103.05)
AUC _{0-t} , ng.h/mL	39	9,707.13	9,601.75	101.10 (99.05 – 103.19)
<u>Metformin</u>				
C _{max} , ng/mL	41	1,035.23	1,038.15	99.72 (95.03 – 104.63)
AUC _{0-∞} , ng.h/mL	40	11,083.21	11,407.87	97.15 (93.26 – 101.22)
AUC _{0-t} , ng.h/mL	37	11,286.97	11,492.95	98.21 (94.28 – 102.29)

N = maximum number of subjects with data.

Food effect was similar to Metformin XR

Parameter	Geometric Mean		Geometric Mean Ratio, % (90% CI)
	Fed (Test) N=24	Fasted (Reference) N=24	
		<u>Canagliflozin</u>	
C_{max} (ng/mL)	1,241.78	1,408.34	88.17 (79.53; 97.75)
$AUC_{0-\infty}$ (ng·h/mL)	12,455.18	11,956.54	104.17 (100.81; 107.64)
AUC_{0-t} (ng·h/mL)	12,782.49	12,232.88	104.49 (101.20; 107.89)
		<u>Metformin</u>	
C_{min} (ng/mL)	917.15	811.45	113.03 (98.64; 129.51)
$AUC_{0-\infty}$ (ng·h/mL)	10,607.86	6,181.44	171.61 (152.83; 192.70)
AUC_{0-t} (ng·h/mL) ^a	10,927.94	6,804.15	160.61 (143.20; 180.13)

^a n=20

- Proposed use: CANA/MET XR FDC tablets be administered with the morning meal

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No evidence of dose dumping when administered with food in the repeated dose study

Metformin PK Parameters from Study DIA1042

PK Parameter	CANA/MET XR FDC (2 x [150/1,000 mg]) (Day 1) n=12	CANA/MET XR FDC (2 x [150/1,000 mg]) (Day 7) n=10 ^a
	C_{max} (ng/mL)	1,434 (285)
$C_{max,ss}$ (ng/mL)	NA	1,581 (251)
$C_{min,ss}$ (ng/mL)	NA	183 (54.8)
t_{max} (h) ^b	10.0 (4.00 – 10.0)	8.00 (4.00 – 12.0)
AUC_{0-ss} (ng·h/mL)	16,604 (3,282)	NA
AUC_{0-t} (ng·h/mL)	NA	19,386 (3,454)
$t_{1/2}$ (h)	NA	7.14 (0.730)
Acc Ratio ^c	NA	1.18 (0.231)

^a Two subjects did not complete the required dinner meal and were excluded from the analyses.

^b Median (range)

^c Based on AUC (AUC_{0-ss}/AUC_{0-t})

NA = Not applicable

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No evidence of dose dumping when administered with food in the repeated dose study

Canagliflozin PK Parameters from Study DIA1042

PK Parameter	CANA/MET XR FDC (2 x [150/1,000 mg]) (Day 1) n=12	CANA/MET XR FDC (2 x [150/1,000 mg]) (Day 7) n=10 ^a
C _{max} (ng/mL)	2,318 (565)	NA
C _{max,ss} (ng/mL)	NA	3,078 (464)
C _{min,ss} (ng/mL)	NA	416 (109)
t _{max} (h) ^b	2.50 (1.50 – 8.00)	1.75 (1.50 – 4.00)
AUC _{τ,0d} (ng.h/mL)	19,505 (2,598)	NA
AUC _{τ,ss} (ng.h/mL)	NA	26,320 (3,672)
t _{1/2} (h)	NA	17.6 (5.52)
Acc Ratio ^c	NA	1.36 (0.143)

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Review Focus

- Do the results of BE studies support sponsor's claim for CANA/MET XR FDC?
 - adequacy of data to support bridging to **individual components**
 - adequacy of data to support food effect claim
 - specifics of data analysis – data exclusions and analysis methods

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Filing Status and Consults

- **Recommendation:** NDA 205879 is *fileable*
 - Raw PK data has been submitted for pivotal BE studies
 - Bioanalytical and method validation reports for the pivotal BE studies
 - Proposed product labeling
 - Clinically-tested formulation in the BE pivotal studies is the same as the to-be-marketed formulation

- **OSIS consult:**
 - Yes, for the clinical and analytical sites for pivotal BE study at highest strength.

- **Request for Sponsor:**
 - None

Filing Memo

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes No

If the NDA/BLA is not fileable from the clinical pharmacology 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.

Comments to Sponsor:

None

Renu Singh 13 Jan, 2016

Reviewing Clinical Pharmacologist Date

Manoj Khurana 13 Jan, 2016

Acting Team Leader Date

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

/s/

RENU SINGH
01/13/2016

MANOJ KHURANA
01/13/2016