CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204042	Submission Date(s): 5/31/2012
Brand Name:	Invokana
Generic Name	Canagliflozin (JNJ-28431754)
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Janssen Research and Development LLC
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Immediate Release Tablets: 100 mg and 300 mg
Proposed Indication	An adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes mellitus

The purpose of this document is to include reference to the sections in the review where risk-benefit in moderate renal impairment is discussed and to clarify the subgroup of moderate renal impairment where OCP review team is not recommending canagliflozin.

Page 54 currently states:

- *The sponsor has proposed no dose adjustment in mild renal impairment which is acceptable. The sponsor indicates that higher incidence of adverse events related to reduction in intravascular volume was observed in patients with moderate renal impairment and has proposed a starting dose of 100 mg for these patients. The UGE in this group is considerably reduced. Consistent with the reduced pharmacodynamic action of canagliflozin in renal impairment, the efficacy was also decreased in moderate renal impaired subjects as discussed in Section 2. Considering the marginal efficacy response as well as higher incidence of adverse events observed in this group of patients, this reviewer recommends that canagliflozin be not used in moderate renal impairment. Canagliflozin is not recommended for severe renal impaired with ESRD patients or on dialysis as efficacy is not expected.*

Page 54: The paragraph should read:

- *The sponsor has proposed no dose adjustment in mild renal impairment which is acceptable. The sponsor indicates that higher incidence of adverse events related to reduction in intravascular volume was observed in patients with moderate renal impairment and has proposed a starting dose of 100 mg for these patients. The UGE in this group is considerably reduced. Consistent with the reduced pharmacodynamic action of canagliflozin in renal impairment, the efficacy was also decreased in moderate renal impaired subjects as discussed in Section 2.3 and Summary of clinical pharmacology findings. Post-hoc analysis of efficacy data for two subgroups in this population (eGFR < 40 and >= 40 mL/min/1.73 m2; separated based on median eGFR), revealed that efficacy seems to be driven by >=40 mL/min/1.73m2 subgroup. Efficacy was not evident in the < 40 mL/min/1,73m2 group in comparison to placebo. Comparison of percentage*

change in renal function (i.e., eGFR) from baseline between treatment groups showed a higher proportion of patients with decrease in eGFR and a larger magnitude of decline in eGFR in patients receiving canagliflozin compared to placebo, in both eGFR<40 and >=40 mL/min/1.73m^2 groups. Considering the marginal efficacy response as well as higher incidence of adverse events observed, this reviewer recommends that canagliflozin be not used in moderate renal impairment (eGFR < 40 mL/min/1.73 m^2). Canagliflozin is not recommended for severe renal impaired with ESRD patients or on dialysis as efficacy is not expected.

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/s/

JAYABHARATHI VAIDYANATHAN
02/12/2013

LOKESH JAIN
02/12/2013

ONDQA BIOPHARMACEUTICS REVIEW ADDENDUM

NDA#:	204-042
Submission Date:	February 8, 2013
Brand Name:	Invokana®
Generic Name:	Canagliflozin (JNJ-28431754)
Formulation:	Film-coated tablets
Strength:	100 mg and 300 mg
Sponsor:	Janssen Research and Development, LLC.
Biopharmaceutics Reviewer:	Houda Mahayni, Ph.D.
Acting Biopharmaceutics Team Leader:	John Z. Duan, Ph.D.
Submission Type:	Response to FDA Information Request

INTRODUCTION

This is an addendum to the Biopharmaceutics review for NDA 204-042 signed off in DARRTS on February 1, 2013, in which FDA requested the Applicant to revise the dissolution acceptance criterion and to provide comparative dissolution data to support the bridge between the clinical (non-debossed) and the to-be-marketed (TBM) tablets (debossed). The following information request was communicated to the Applicant on February 4, 2013:

1. Based on the dissolution data for your product, an acceptance criterion of Q = (b) (4) at 20 minutes should be implemented. Provide a revised specification table for your drug product with the updated dissolution acceptance criterion.

2. To support the bridge between the clinical (non-debossed) and the TBM (debossed) tablets, provide the dissolution profile comparisons and f2 data.

FDA and the Applicant had a teleconference on February 5, 2013, and the Applicant agreed to revise the dissolution acceptance criterion to Q (b) (4) at 20 minutes, and committed to update the drug product specification to reflect the change in the acceptance criterion. Also, the Applicant stated that if a change in the dissolution acceptance criterion is warranted based on additional data collected from the long term stability studies, a request with a rationale to change the dissolution acceptance criterion will be submitted.

The Applicant agreed to provide the requested comparative dissolution profiles to support the bridge between the clinical (non-debossed) and the TBM (debossed) tablets. The Applicant stated that the requested information will be submitted to FDA on February 8, 2013.

In response to item 1 above, the Applicant submitted a revised drug product specification table to reflect the revised dissolution acceptance criterion from Q= (b) (4) to Q (b) (4) in 20 minutes.

In response to item 2 above, the Applicant stated that subsequent to the call on February 5, 2013, it was confirmed that all Phase 3 clinical batches were debossed. The initial Phase 3 clinical batches, manufactured at (b) (4) were debossed with (b) (4) on one side and (b) (4) on the other, while the later Phase 3 clinical batches, manufactured at the commercial manufacturing facility at Gurabo, PR, were debossed with "CFZ" on one side and "100" or "300" on the other, depending on the strength. Also, the registration stability (to-be-marketed) tablets manufactured at Gurabo are debossed with "CFZ" on one side and "100" or "300" on the other.

The comparative dissolution data provided below were generated using the proposed regulatory method. Figure 1 and Figure 2 provide the comparative dissolution profiles of the 100 mg and 300 mg clinical batches manufactured at the clinical manufacturing facility in (b) (4) and debossed with (b) (4) on one side and (b) (4) on the other, and clinical/registration batches manufactured at the proposed commercial manufacturing facility in Gurabo, PR and debossed with "CFZ" on one side and "100" or "300" on the other, depending on the strength. Table 1 and Table 2 present the corresponding data and f2 values for each figure.

Figure 1: Comparative Dissolution Profiles for 100-mg Representative Phase 3 Clinical (PD3245) and Clinical/Registration (0HG2281-X) Batches

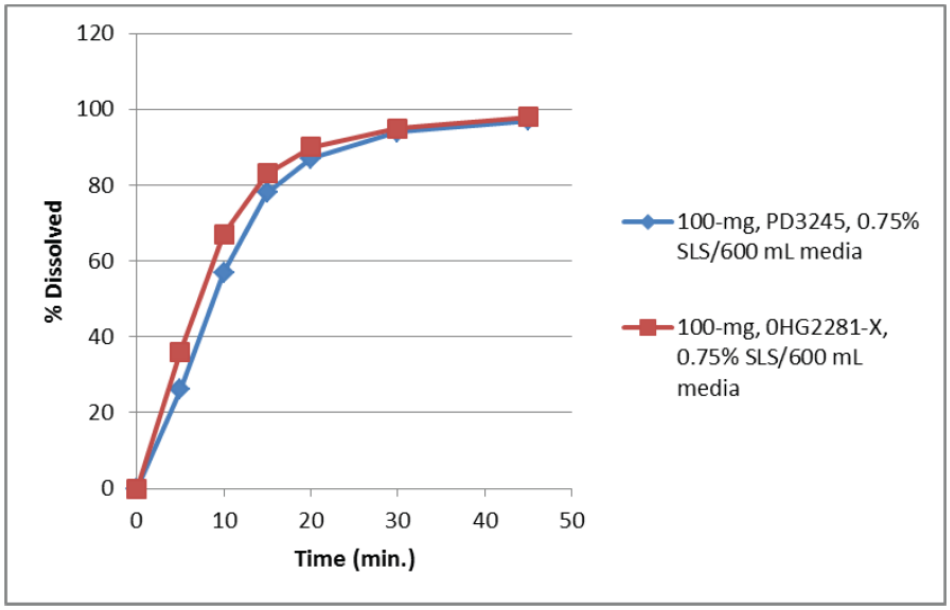

Table 1: Results of f2 Computation for the Average Dissolution Profiles Presented in Figure 1 (n=6)

Time Point (min)	Test Batch 0HG2281-X	Reference Batch PD3245
5	36	26
10	67	57
15	83	78
20	90	87
30	95	94
45	98	97
Total:	538	568
f2 Value	Criterion	Pass/Fail
60	≥50	Pass

Figure 2: Comparative Dissolution Profiles for 300-mg Representative Phase 3 Clinical (PD3251) and Clinical/Registration (0HG2279-X) Batches

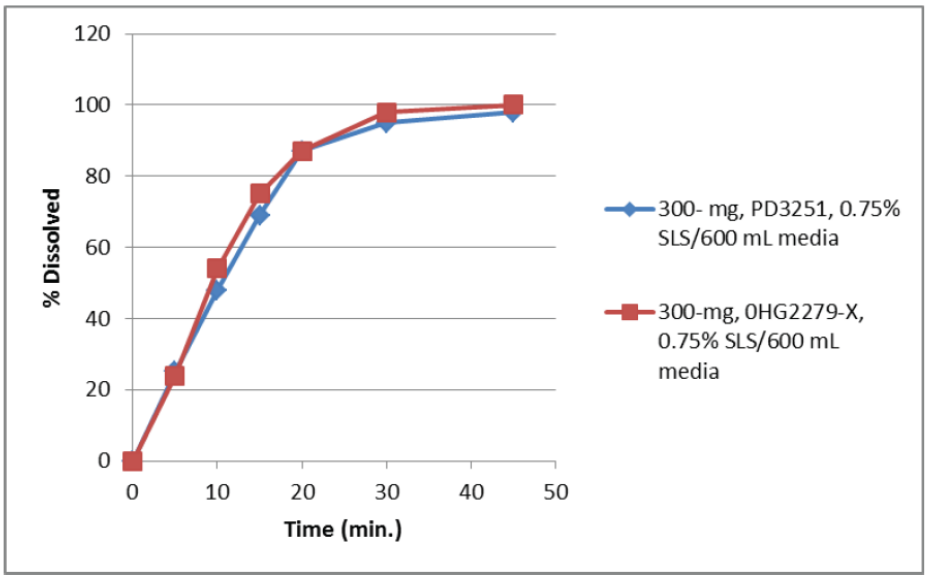

Table 2: Results of f2 Computation for the Average Dissolution Profiles Presented in Figure 2 (n=6)

Time Point (min)	Test Batch 0HG2279-X	Reference Batch PD3251
5	24	25
10	54	48
15	75	69
20	87	87
30	98	95
45	100	98
Total:	538	522
f2 Value	Criterion	Pass/Fail
70	≥50	Pass

REVIEWER'S COMMENTS

The Applicant fulfilled their commitment to revise the dissolution acceptance criterion and update the drug product specification table to reflect the change in the dissolution acceptance criterion from Q= (b) (4) to Q (b) (4) in 20 minutes.

The clinical batches manufactured at (b) (4) and the clinical/registration batches (representative of the TBM tablets) manufactured at Gurabo met the similarity factor (f2≥ 50) and are considered similar.

The following typographical error to the dissolution acceptance criterion was made in the Biopharmaceutics review submitted in DARRTS on February 1, 2013: Q= (b) (4) in 20 minutes. **The correction is Q= (b) (4) in 20 minutes**. It was noted that there are three places in the review where FDA recommended revising the dissolution acceptance

criteria to Q = (b) (4) in 20 minutes instead of Q = (b) (4) in 20 minutes. The three typos are found on pages 3, 4, and 45 in the review.

RECOMMENDATION

ONDQA-Biopharmaceutics team reviewed the Applicant's response to FDA Information Request and found the response acceptable.

From the Biopharmaceutics perspective, NDA 204-042 for Canagliflozin film-coated tablet (100 mg and 300 mg) is recommended for APPROVAL.

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

John Z. Duan, Ph.D.
Acting Biopharmaceutics Team Leader
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cc: *DARRTS CC List: RLostritto; ADorantes*

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/s/

HOUDA MAHAYNI
02/11/2013

JOHN Z DUAN
02/11/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204042	Submission Date(s): 5/31/2012
Brand Name	Invokana
Generic Name	Canagliflozin (JNJ-28431754)
OCP Division	Clinical Pharmacology -2
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Sponsor	Janssen Research and Development LLC
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Immediate Release Tablets: 100 mg and 300 mg
Proposed Indication	An adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes mellitus
Clinical Pharmacology Review Team	Jayabharathi Vaidyanathan, Manoj Khurana, Suryanarayana Sista, Lokesh Jain, Anshu Marathe, Nitin Mehrotra, Lyle Canida, and Michael Pacanowski

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1 Executive Summary

Canagliflozin is being developed by Janssen Research & Development in collaboration with Mitsubishi Tanabe Pharma Corporation (MTPC). Canagliflozin is a new molecular entity that belongs to the sodium-glucose cotransporter-2 (SGLT2) inhibitor class of anti-diabetic agents. There are currently no SGLT2 inhibitors approved by the FDA. Dapagliflozin (NDA 202293), another SGLT2 inhibitor received a Complete Response (CR) action from the Agency. If approved, canagliflozin will be the first in the class of SGLT2 inhibitors.

Canagliflozin is intended to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 5/31/12 under NDA 204042 and recommend approval with the following recommendations. A Required Office Level OCP briefing was held on January 29, 2013 to discuss the review team's recommendations. OCP recommends the following regulatory and labeling actions:

I Dosing in type 2 diabetic patients with normal renal function (eGFR > 90 mL/min/1.73 m^2) and mild renal impairment (eGFR = 60-90 mL/min/1.73 m^2):

a) The sponsor proposes canagliflozin 100 mg **or** 300 mg be administered prior to the first major meal of the day.
b) In the package insert, Section 2.1 Recommended Dosing, there is no specific guideline for prescribers to decide on which dose to initiate in patients who are not at an elevated risk of adverse reactions related to reduced intracellular volume. OCP is of the opinion that this dosing recommendation should be more specific as to which patient should be started at the 100 mg or the 300 mg dose.
c) Both 100 mg and 300 mg QD are efficacious with the 300 mg providing a numerically higher response in terms of lowering of HbA1c in monotherapy and combination therapy trials. The slight incremental benefit of using 300 mg QD over 100 mg QD must be counterbalanced against observed dose-dependent adverse events and changes in fluid and electrolyte balance (e.g., volume depletion-related adverse events, renal function changes, mineral and electrolyte changes). Most of these changes were observed within 3-6 weeks of initiating therapy, with higher incidence at the higher dose, i.e., 300 mg QD. These adverse events regressed over time; although, in many cases did not return to patients' baseline levels over the duration of clinical trials (i.e., 26 or 52 weeks).
d) OCP review team therefore, recommends a titration-based dosing strategy based on overall benefit-risk of canagliflozin in treatment of type 2 diabetes, given that efficacy and safety information for both doses are available:

- Starting dose of 100 mg QD in all patients.
- Titrate to 300 mg based on individual patient's tolerability and need of further glycemic control.

II Dosing in moderate renal impaired patients with an estimated glomerular filtration rate of 30-60 mL/min/1.73 m^2:

a) Canagliflozin acts as an inhibitor of renal SGLT2; activity of canagliflozin is dependent on the renal function of patients. The sponsor conducted a dedicated efficacy-safety trial in type 2 diabetes patients with moderate renal impairment.

b) Based on canagliflozin's mechanism of action, we hypothesized there would be a subset of patients with renal dysfunction who would exhibit diminished responses. There appears to be an attenuated HbA1c response in patients with moderate renal impairment (compared to those with normal renal function or mild renal impairment [eGFR ≥ 60 mL/min/1.73m2]) based on cross-study evaluation.

c) A post-hoc analysis was conducted for the dedicated trial in patients with moderate renal impairment, Trial DIA3004, evaluating efficacy in subgroups using an eGFR cut-off of 40 mL/min/1.73m^2, which was the median value of eGFR in this trial. This analysis demonstrated that the efficacy in patients with moderate renal impairment was primarily driven by the subjects with baseline eGFR ≥ 40 mL/min/1.73m^2. In eGFR<40 mL/min/1.73m^2 group, reduction in HbA1c in patients receiving canagliflozin 100 mg or 300 mg did not appear to be different compared to placebo.

d) We also conducted a renal safety evaluation of Trial DIA3004. This analysis demonstrated that, in eGFR≥40 mL/min/1.73m^2 group, a 10-12 fold higher percentage of patients had >30% reduction in eGFR from baseline with canagliflozin compared to placebo; in patients with eGFR<40 mL/min/1.73m^2, risk of >30% reduction in eGFR was 2-3 fold higher for canagliflozin compared to placebo. There were 3 cases of >50% reduction in eGFR from baseline in Trial DIA3004, all of which occurred in patients receiving canagliflozin. Further comparison of percentage change in eGFR from baseline between treatment groups based on baseline renal function showed a higher proportion of patients with decrease in renal function (i.e., eGFR) and a larger magnitude of decline in eGFR in patients receiving canagliflozin compared to placebo, in both eGFR<40 mL/min/1.73m^2 and eGFR ≥40 mL/min/1.73m^2groups. However, these eGFR changes appear to be transient and on an average regressed by week 26, although eGFR did not return to baseline in majority of subjects.

e) Given the lower response of canagliflozin in eGFR<40 mL/min/1.73m^2 group and the increased risk of decline in renal function (eGFR) from baseline, we consider benefit-risk of canagliflozin to be unfavorable in eGFR<40 mL/min/1.73m^2 group. Although similar risks were present in eGFR>=40 mL/min/1.73m^2 group, these patients benefit at both 100 and 300 mg canagliflozin doses compared to placebo. Therefore, we consider benefit-risk of canagliflozin to be favorable in eGFR>=40 mL/min/1.73m^2 group when administered with caution.

f) OCP review team therefore, recommends:

In patients with eGFR >=40 - 60 mL/min/1.73m^2

- Starting dose: 100 mg QD in patients
- Labeling explicitly cautioning on the use of the 300 mg dose

In patients with eGFR <40 mL/min/1.73m^2

- Do not use canagliflozin because of unfavorable benefit-to-risk ratio

III Renal function, volume status, and electrolyte balance should be closely monitored in elderly and other patients with high risk of volume depletion (e.g., on loop diuretics) especially when the dose is increased from 100 mg QD to 300 mg QD.

IV ***Co-administration with rifampin:*** Canagliflozin exposure is significantly lowered in the presence of rifampin. It is recommended that patients well managed on 100 mg canagliflozin be considered for the higher dose when a potent UGT inducer (like rifampin) is initiated.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Table 1 summarizes the key pharmacokinetic properties of canagliflozin.

Table 1: Highlights of Clinical Pharmacology

Proposed dose	100 mg or 300 mg once daily
Absorption	• Median Tmax – 1-2 h • Dose-proportional PK in the 50- 300 mg dose range • No effect of food on PK • Accumulation ratio at steady-state ranged from 1.29 – 1.36 • Absolute bioavailability ~65% • Steady-state reached after 4-5 days of once daily dosing • No time-dependency of PK • Unchanged canagliflozin is the main drug-related component in the plasma
Distribution	• 98.3% to 99.2% bound to plasma proteins, predominantly to albumin • Mean Vss: 119L following single intravenous

	injection in healthy subjects, indicating extensive tissue distribution
Metabolism	• The main metabolic pathway in human hepatocytes was O-glucuronidation of canagliflozin to the O-glucuronide metabolite M7 (formed by UGT1A9) and a minor O-glucuronide, M5 (formed by UGT2B4).
Elimination	• Primary route is fecal (60.4% of total radioactivity) indicating biliary excretion as a major elimination pathway • Elimination in urine accounted for 32.5% of radioactivity with less than 1% excreted intact as parent • Apparent terminal half-life: 10.6 h for the 100 mg and 13.1 h for the 300 mg dose, respectively
Intrinsic Factors	• Age: No effect on PK based on population PK analysis • Gender: No effect on PK based on population PK analysis • Race: No effect on PK based on population PK analysis • Body weight: No effect on PK based on population PK analysis • Renal and Hepatic impairment: see below
Formulation	• To-be-marketed formulation is identical to the Phase 3 clinical trial formulation

Dose-response relationship for effectiveness:
The dose-response is evident among 100 mg and 300 mg QD canagliflozin treatment regimens based on efficacy data. The time-profile for the LS mean change from baseline in HbA1c for one of the Phase 3 trial (monotherapy trial DIA3005) is shown in Figure 1 below. A clear separation in mean HbA1c reduction from baseline over time profile was observed between the two active treatment arms (canagliflozin; 100 mg and 300 mg) and the placebo group (Figure 1). The HbA1c reduction appeared to reach plateau by Week 26. Similar results were evident from the add-on therapy trials.

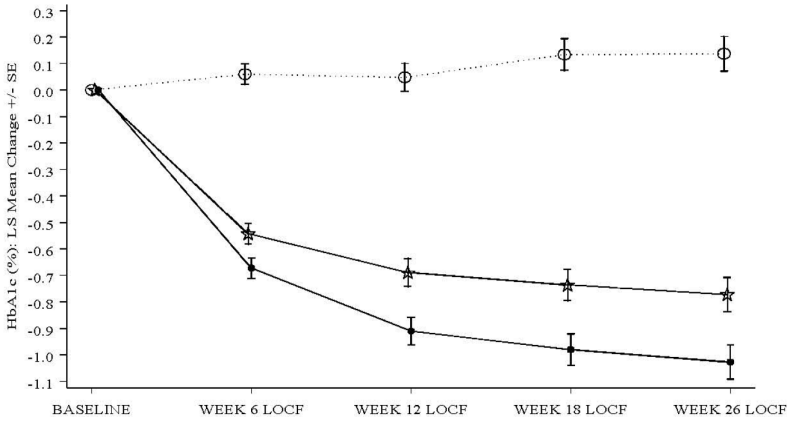


Figure 1: Time-profiles for mean (±SE) change from baseline in HbA1c in Phase 3 monotherapy trial DIA3005

[*Source: Sponsor's Figure 4 in DIA3005 Study Report, Page 85]*

Dose-response for safety:

Impact on renal function: Canagliflozin lowered the eGFR from baseline in a both, dose and baseline renal function dependent manner. Effect of canagliflozin on renal function was evaluated based on a longitudinal change from baseline in eGFR, and by evaluating the reduction in eGFR as a function of baseline renal function.

Figure 2 shows the longitudinal change from baseline in eGFR by treatment for pooled placebo controlled trials (DS1: Trials DIA3002, DIA3005, DIA3006, and DIA3012). Based on the pooled placebo controlled phase 3 trial data, for mean decrease from baseline in eGFR, nadir was observed by Week 6, with subsequent increases at Week 26 from the nadir value. At Week 26, mean percent changes from baseline of -1.8% and -3.0% in the canagliflozin 100 mg and 300 mg groups, respectively, and -0.5% in the placebo group was seen.

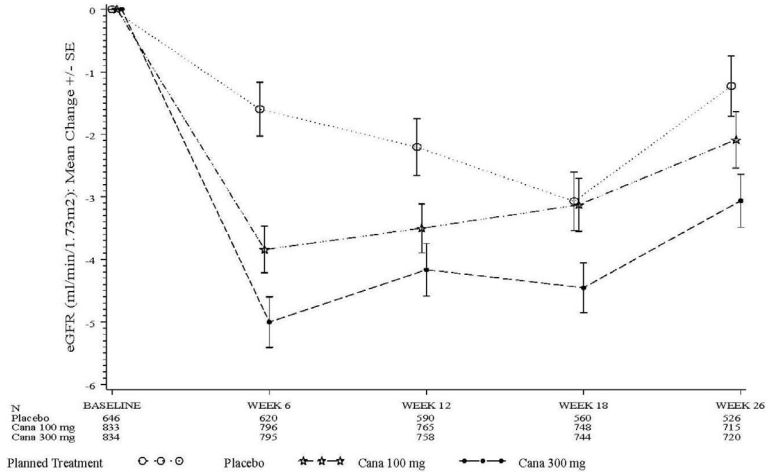


Figure 2: Mean change (+/-SE) in eGFR (mL/min/1.73m2) from baseline over time (ISS Phase 3 Placebo-Controlled Studies Dataset DS1: Safety Analysis Set).

[Source: Summary of Clinical Safety, Figure 17, Page 242]

Impact on safety related laboratory markers and volume depletion adverse events: Canagliflozin treatment results in dose-dependant increase in blood urea nitrogen, and serum electrolytes (magnesium, potassium, and phosphate), and incidences of volume depletion adverse events (Section 2.3.4). The effect on hematocrit was similar for both 100 and 300 mg QD doses. The proportion of subjects with adverse events (AEs) related to volume depletion were increased, specifically in the presence of moderate renal impairment, age>=65, and concomitant use of loop diuretics (Section 2.3.4).

Benefit-risk in renal impairment:

Since a trend of attenuation in efficacy with increased severity of renal impairment was observed based on cross-study comparisons, we performed a post-hoc analysis for benefit-risk in patients with moderate renal impairment to identify if there are any subgroup of population within these patients that may benefit from canagliflozin.

Efficacy: A post-hoc analysis was conducted for trial DIA3004 (trial conducted in patients with moderate renal impairment), evaluating efficacy in subgroups with an eGFR cut-off of 40 mL/min/1.73m^2 (i.e., the median eGFR value in trial 3004).

As shown in the Figure 3 below, in eGFR<40 mL/min/1.73m^2 group, reduction in HbA1c in patients receiving canagliflozin 100 mg or 300 mg does not appear to be different compared to placebo. This is expected based on canagliflozin's mechanism of action. Mechanistic pharmacodynamic studies demonstrated that the lower urinary glucose response to canagliflozin in renal impaired subjects is related to less filtered glucose (due to lower GFR) and less effect of canagliflozin in reducing RTG.

In patients with eGFR>=40 mL/min/1.73m^2, an attenuated response for reduction in HbA1c is observed compared to subjects with normal renal function or mild renal impairment based on cross-study comparisons and post-hoc analysis.

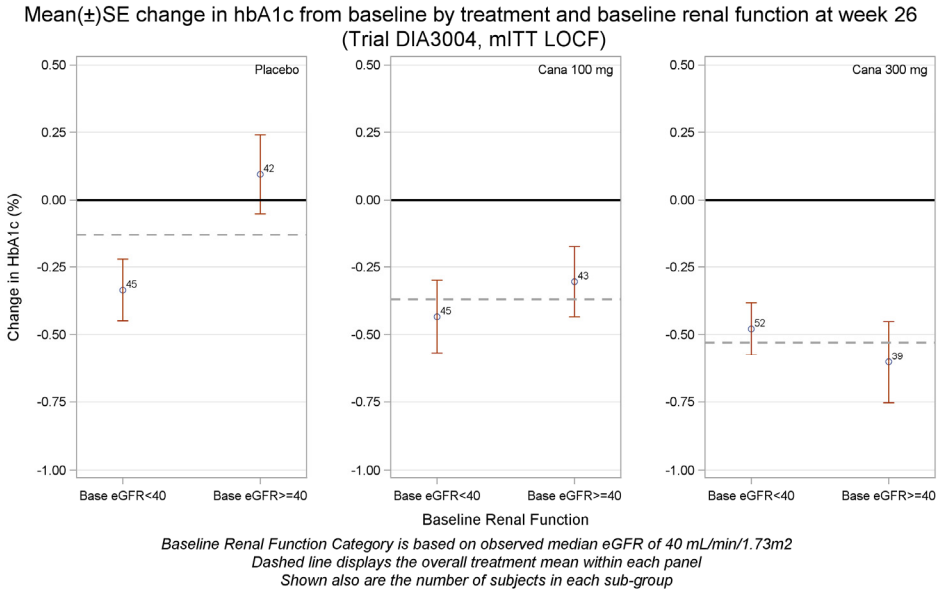


Figure 3: Change in HbA1c is affected by baseline renal function and treatment in type 2 diabetes mellitus subjects with moderate renal impairment (DIA3004)

Safety Similar to efficacy, a post-hoc analysis was also conducted to compare the safety in eGFR<40 mL/min/1.73m^2 and eGFR>=40 mL/min/1.73m^2 subgroups.

Patients with >30% and >50% Decline In Renal Function (changes in eGFR) from Baseline

- In eGFR>=40 mL/min/1.73m^2 group, percentage of patients with >30% reduction in eGFR from baseline (Table 2) were 10-12-fold higher with canagliflozin treatment compared to placebo. In eGFR<40 mL/min/1.73m^2 group, treatment with canagliflozin further increased the risk of reduction in eGFR by about 2-3-fold compared to placebo. This indicates that patients who are receiving canagliflozin are more susceptible to decline in renal function in patients with moderate renal impairment.

- Comparison of placebo groups in eGFR<40 and eGFR >=40 groups show that patients with more compromised renal function at baseline are at about 2.5 fold higher risk of further reduction (i.e., >30% reduction from baseline) in eGFR. To note is that these reductions do regress over time although not to baseline levels.

- There were only 3 patients with > 50% decline in eGFR from baseline in Study DIA 3004. However, it is worth noting that all three cases were observed in patients receiving canagliflozin (Table 3).

- Greater than 30% reduction in eGFR for a patient with baseline eGFR of <40 mL/min/1.73m^2, may bring that patient into a severe renal impairment category,

which will not only limit the use of canagliflozin but also other drugs which are only approved for moderate renal impairment and not for severe renal impairment.

- However, the same reduction of 30% in eGFR in a patient with baseline eGFR of >=40 mL/min/1.73m^2 will likely keep that patient into moderate renal impairment category and thus not limit the use of canaglifozin or other approved treatments.

Table 2. Number of patients with >30% reduction in eGFR from baseline at any time point based on Trial DIA3004

>30% reduction in eGFR from baseline						
		eGFR <40			**eGFR >=40**	
	Placebo	**100 mg**	**300 mg**	**Placebo**	**100 mg**	**300 mg**
number of events	3	7	10	1	9	10
total patients	45	47	52	42	43	39
%	6.67	14.89	19.23	2.38	20.93	25.64

Table 3. Number of patients with >50% reduction in eGFR from baseline based on Trial DIA3004

>50% reduction in eGFR from baseline						
		eGFR <40			**eGFR >=40**	
	Placebo	**100 mg**	**300 mg**	**Placebo**	**100 mg**	**300 mg**
number of events	0	0	1	0	1	1
total patients	45	47	52	42	43	39
%	0	0	1.92	0.00	2.33	2.56

Patients with Renal Impairment Related Adverse Events

We also searched the number of patients with renal related adverse events in the pooled data set for patients with moderate renal impairment (combined data from studies DIA 3004, 3005, 3008 and 3010). Following terms were used in the database search: 'Acute prerenal failure' 'Azotaemia' 'Diabetic nephropathy' 'Nephritis' 'Nephropathy' 'Renal failure' 'Oliguria' 'Renal failure acute' 'Renal impairment' 'Renal tubular necrosis' 'Renal atrophy'. These terms were similar to that used for the analysis presented at the advisory committee meeting. While interpreting results from this analysis it should be noted that there were limited number of events in the subset of patients with moderate renal impairment.

- In eGFR>=40 mL/min/1.73m^2 group, we observe about a 2-fold increase in renal function related adverse events following treatment with canagliflozin compared to placebo (Table 4).

- Comparison of placebo groups in eGFR<40 and eGFR >=40 groups show about a 2 fold increase in renal function related adverse events in patients with more compromised renal function (i.e., eGFR<40). Infact, the % of renal function related adverse events in placebo with eGFR<40 are higher than that for eGFR >=40 patients receiving canagliflozin. This suggests that patients with eGFR<40 inherently may be at higher risk for renal function related adverse events.

- In eGFR<40 mL/min/1.73m^2 group, patients receiving canagliflozin had a comparable or higher risk of renal function related adverse events compared to placebo.

- Comparison of renal function related adverse events between eGFR<40 and eGFR >=40 groups, show a relatively higher risk irrespective of placebo or canagliflozin treatment.

Table 4: **Number of patients with renal function related adverse events based on pooled data from trials DIA 3004, 3005, 3008 and 3010 (DS2: Moderate renal impairment dataset)**

Pooled data (DS2)						
		eGFR <40			eGFR >=40	
	placebo	100 mg	300 mg	placebo	100 mg	300 mg
number of events	4	6	4	7	11	12
total patients	67	70	72	316	272	297
%	5.97	8.57	5.56	2.22	4.04	4.04

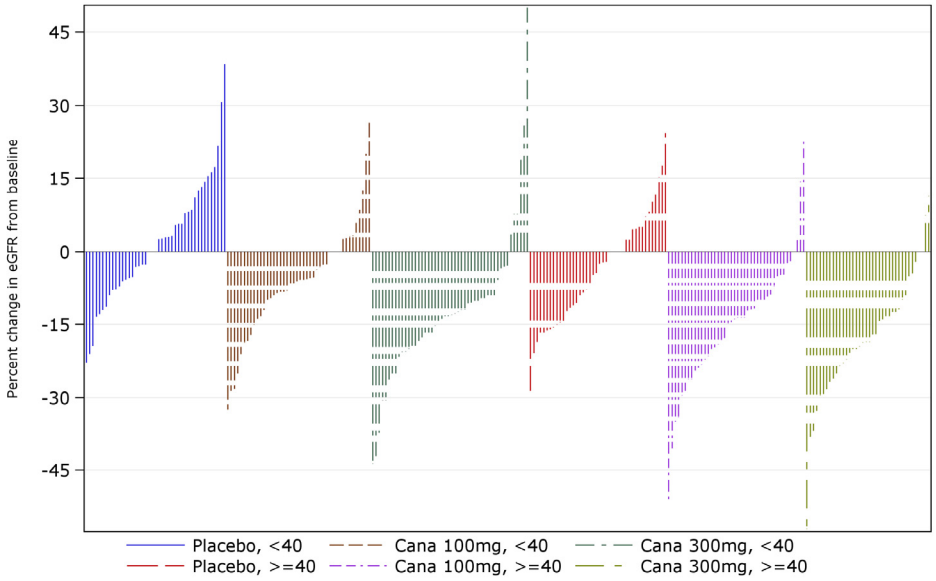
Change in eGFR in Placebo vs. Canagliflozin Treatment Groups

The needle plot in Figure 4 compares the percent decline in eGFR between placebo and canagliflozin treatment groups at week 3 and week 26 based on baseline renal function (eGFR<40 vs. >=40 mL/min/1.73m^2) in patients with moderate renal impairment (Trial DIA3004).

- In eGFR<40 group, more number of patients on canagliflozin treatment had decline in eGFR from baseline compared to placebo and the magnitude of decline was also higher than placebo. Similar differences between placebo and treatment groups were also observed for eGFR>=40 group.
- At week 3, comparison of eGFR<40 and eGFR>=40 groups show that both the magnitude of percent reduction in eGFR and number of subjects with decline in eGFR is higher for eGFR>=40 group.

- The decline in renal function (eGFR) appeared to regress over time (i.e., by week 26). Although, similar to week 3, a higher number of patients in treatment group had decline in eGFR compared to placebo, but on an average the magnitude of decline in eGFR was relatively low at week 26.

Week 3:



Week 26:

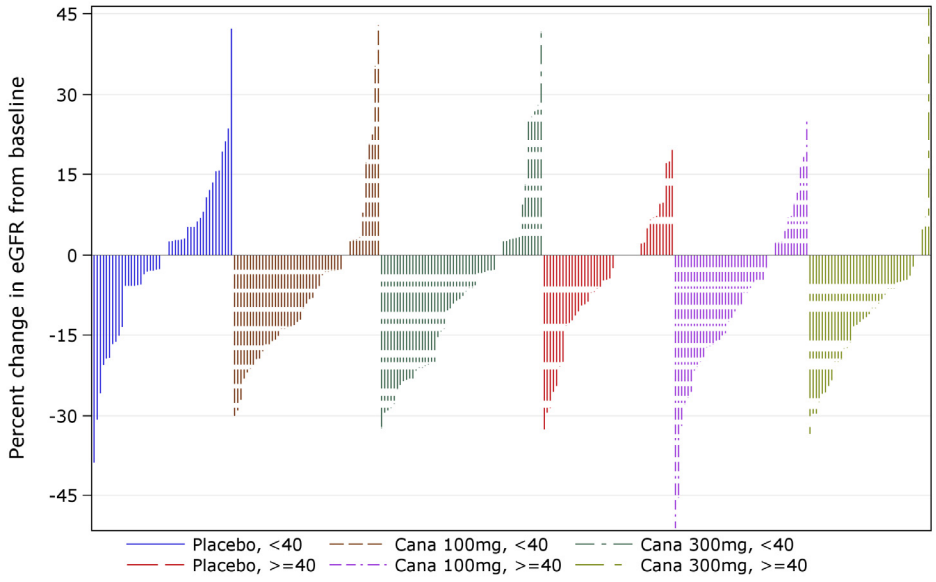


Figure 4. Needle plot comparing percent decline in eGFR in Placebo vs. Treatment groups based on baseline renal function category (Study 3004) at Week 3 and Week 26. Each vertical line represents one patient.

Benefit-Risk: Overall we observe that patients with eGFR<40 mL/min/1.73m^2 are inherently at higher risk of renal function related adverse events or further decline in eGFR. Treatment with canagliflozin appears to further increase that risk.

Given that patients with eGFR<40 mL/min/1.73m^2 do not benefit from canagliflozin compared to placebo, we consider benefit-risk of canagliflozin to be unfavorable in eGFR<40 mL/min/1.73m^2 group.

Although similar risks were present in eGFR>=40 mL/min/1.73m^2 group, these patients benefit at both 100 and 300 mg canagliflozin doses compared to placebo. Therefore, we consider benefit-risk of canagliflozin to be favorable in eGFR>=40 mL/min/1.73m^2 group when administered with caution.

Drug-Drug Interaction (DDI): The following two Figures (5 & 6) summarize the impact of drug-drug interactions. Overall, there was no DDI for which a dose-adjustment is needed. The most significant of these interactions were the effect of rifampin on canagliflozin PK and the effect on digoxin PK by canagliflozin.

As shown in Figure 5, there was a 52% reduction in the systemic exposure of canagliflozin in presence of rifampin. This is apparently due to induction of the UGT enzymes responsible for the metabolism of canagliflozin. However, the metabolites levels did not increase as expected, with a 36% increase in the levels of the metabolite, M7 and no increase in M5 levels in presence of rifampin. This suggests that the biliary excretion may also have been induced due to induction of biliary transporters. Also consistent with this speculation is that the M7 and M5 in urine were decreased in presence of rifampin. This reviewer recommends that patients be on the 300 mg canagliflozin dose when rifampin is co-administered since there may be a greater potential for loss of efficacy at the 100 mg dose.

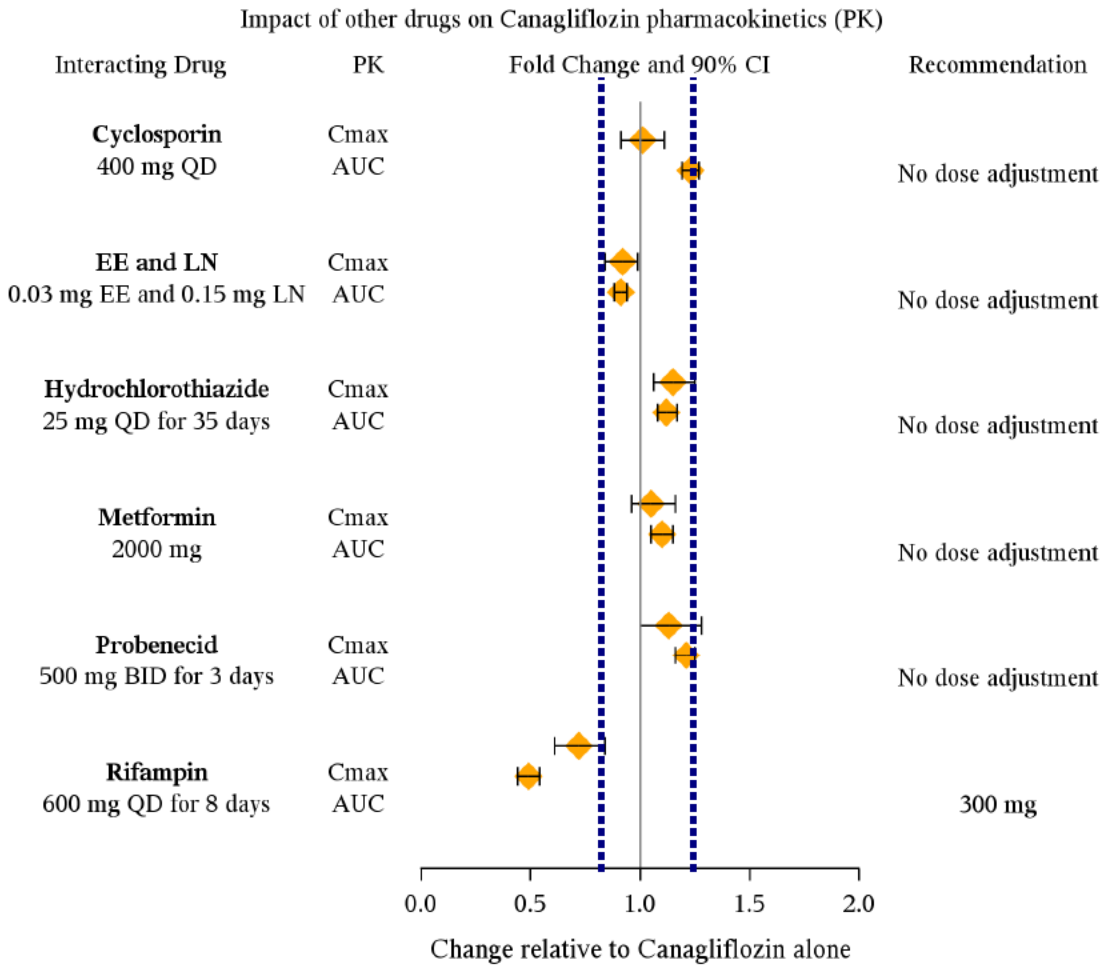


Figure 5: Effect of Drugs on the Pharmacokinetics of Canagliflozin. ***Dashed line indicate the 80%-125% limit***

Mean digoxin trough levels were 18% higher in presence of canagliflozin. The AUC0-24 and Cmax values of digoxin were approximately 20% and 36% higher, respectively, when digoxin was co-administered with canagliflozin compared to when digoxin was administered alone (Figure 6). No subjects exceeded the upper limit of the therapeutic range of digoxin (2.0 ng/mL) beyond the 6-hour time-point. The sponsor's recommendation to monitor digoxin levels when it is co-administered with canagliflozin is acceptable.

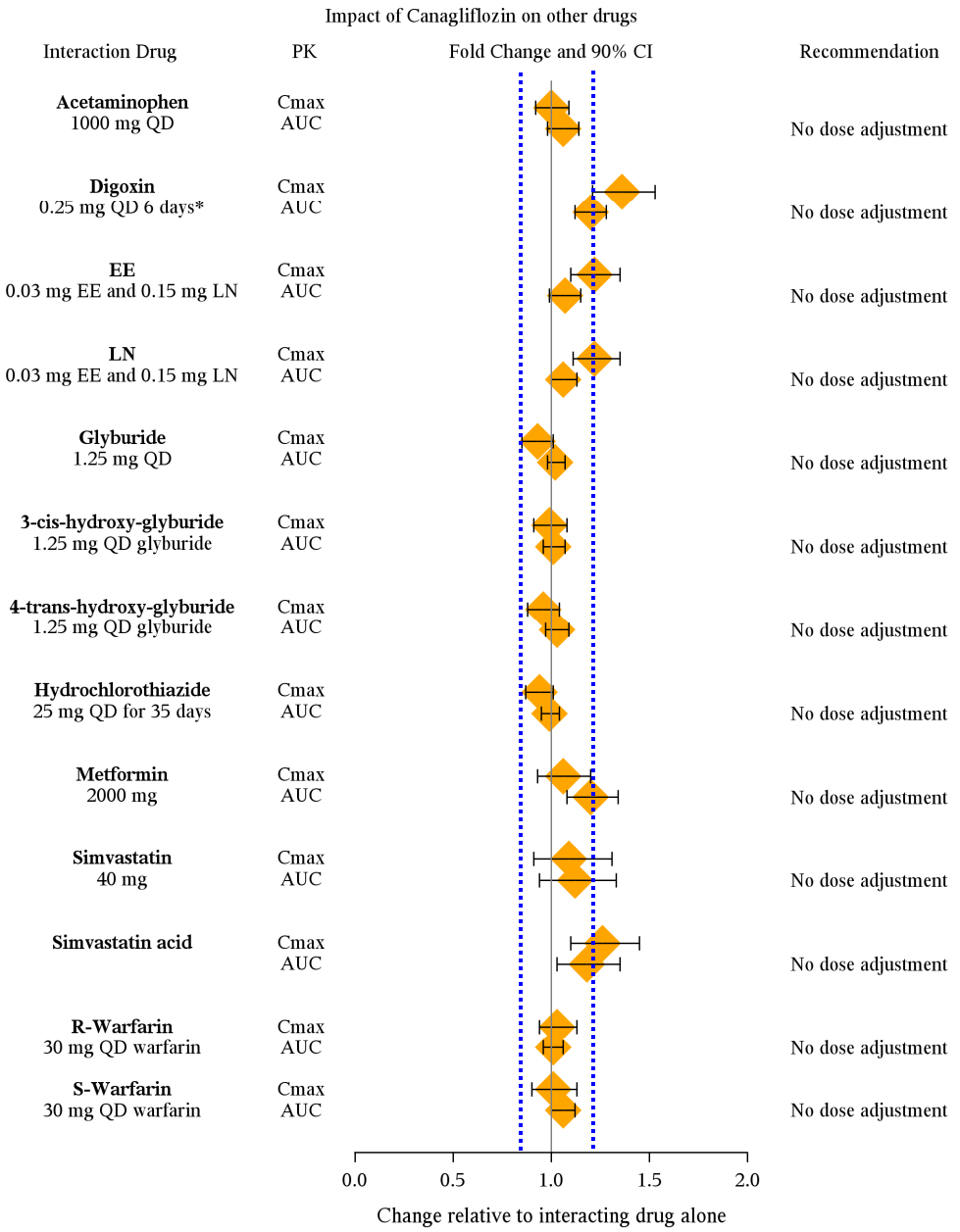


Figure 6: Effect of Canagliflozin on the Pharmacokinetics of Other Drugs. ***Dashed line indicate the 80%-125% limit***

Hepatic Impairment:

Mild or moderate hepatic impairment (Child-Pugh Classes A and B), had no effect on canagliflozin PK (Figure 7). Sponsor's proposal for no dose adjustment of canagliflozin in mild and moderate hepatic impaired patients is acceptable. Effect of severe hepatic impairment on canagliflozin PK was not studied and hence sponsor is not recommending use of canagliflozin in this population. Based on the observations in mild to moderate hepatic impairment, the potential of a significant increase in exposure in severe hepatic

impairment is minimal. Therefore, this reviewer recommends using caution if the drug is used in severe hepatic impairment.

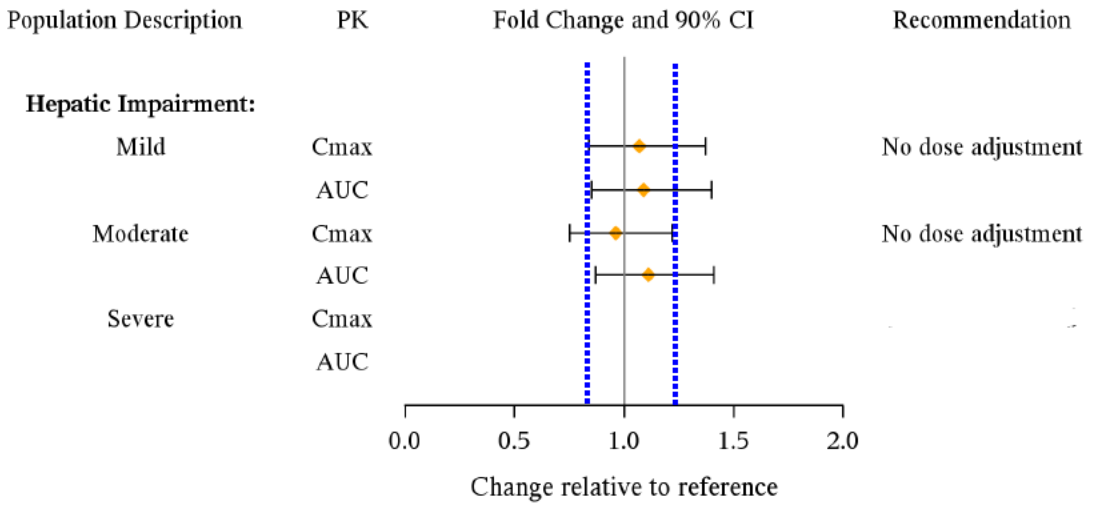


Figure 7: Effect of Hepatic Impairment on Canagliflozin PK. ***Dashed line indicate the 80%-125% limit***

Genetic Variation: Canagliflozin is primarily metabolized by the polymorphic uridine diphosphate glucuronosyltransferase (UGT1A9 and UGT2B4). The sponsor conducted an exploratory pharmacogenomics meta-analysis to assess the impact of UGT1A9*3 variation on canagliflozin trough concentrations. Compared to noncarriers, carriers of the *UGT1A9*3 allele exhibited higher plasma canagliflozin trough concentrations on an average. However, canagliflozin exposures in this subgroup were within the range of exposures observed in noncarriers, and the *1/*3 genotype accounts for little of the overall variability in canagliflozin C_{trough}. UGTB4 genotype did not have any effect on canagliflozin C_{trough} among the 291 subjects with available data, with or without stratification by *UGT1A9* genotype.

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

Canagliflozin is an orally-active inhibitor of human renal SGLT2. Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Canagliflozin tablets 100 mg and 300 mg are the proposed commercial strengths. The sponsor's proposed dosing recommendation is 100 mg or 300 mg to be given once daily.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Canagliflozin is a new molecular entity developed by Janssen Research & Development for the indication of treatment of type 2 diabetes. Canagliflozin belongs to a new class of drugs known as SGLT2 inhibitors. Currently, no SGLT2 inhibitor is approved in the USA. Dapagliflozin, another SGLT2 inhibitor is approved in the European Union, while it received a CR action from the FDA. A standard review status was granted for this NDA. This drug was discussed at a FDA Advisory Committee meeting on January 10, 2013. Discussion at the meeting and comments from the advisory committee members are summarized below. Please see the transcript for details of the committee's discussion.

Discussion on benefit-risk of canagliflozin in moderate renal impaired patients: '*The committee members generally agreed that the benefit-risk profile of canagliflozin in patients with type 2 diabetes and moderate renal impairment should be considered differently from the general population. There was a concern about use in patients since efficacy was decreased with an increased incidence of side effects. The committee members further discussed a discomfort with the relatively small volume of data to support use in this population. Some committee members suggested a need for separate consideration of renal function in the elderly, as exclusion based only on eGFR could eliminate patients who may actually be suitable candidates for treatment with canagliflozin.'*

Discussion on observed fractures in Phase 3 trials and relevance of bone turnover markers: '*The committee agreed that the impact of canagliflozin on bone could not be fully understood from the available data, and that a 52 week assessment likely does not provide sufficient information about this risk. One member suggested that long term studies may be necessary either before or post-marketing to assess the potential clinical impact of these changes. Another committee member suggested that the decrease in bone mineral density could be related to weight loss with canagliflozin, and that it may be expected to plateau. Also, another committee member noted a particular concern in the renally-impaired population, in which hyperphosphatemia and decreased 1,25 dihydroxy vitamin D can also be early features of renal osteodystrophy, and can lead to worse outcomes in this group of patients than in the general patient population. It was also discussed that there could be particular concern with off-label use of canagliflozin in non-type 2 diabetes in younger patients, where changes in bone density during these years could have a more detrimental impact over the course of life.'*

Discussion on the cardio-vascular risk: '*The committee members generally expressed a concern with the relatively limited volume of data to inform this risk, and stated a desire for longer follow-up for cardiovascular endpoints. These members cited some unresolved questions, such as an increased incidence of stroke, increases in low-density cholesterol, and imbalanced MACE+ events at thirty days. These members generally discussed a need for a longer period of exposure, particularly for a drug that treats a chronic disease.*'

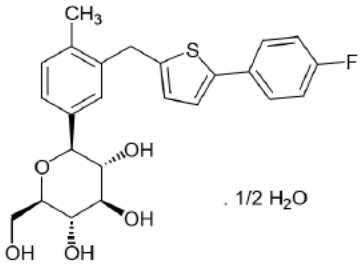
The following voting question was asked;
Vote: Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of canagliflozin for the treatment of Type 2 diabetes mellitus?

Yes: 10
No: 5
Absent: 0

To note: Canagliflozin is also referred in this document as JNJ-28431754.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Table 5: Chemistry and Physicochemical Properties of the Drug Substance

	Canagliflozin
Appearance	**White to off-white powder**
Chemical Name (IUPAC)	(1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate
Molecular Formula	**$C_{24}H_{25}FO_5S.1/2\ H_2O$**
Molecular Weight	**453.53**
Structural Formula	

Solubility	Practically insoluble in aqueous media at all pH
Melting Point:	98.4 ° C
***n*-Octanol/Water Partition Coefficients (Log P) at 20°C at pH 7**	3.44
Isomerism	(b) (4)

Formulation: Canagliflozin is available as oral immediate release film coated tablets at strengths of 100 mg and 300 mg. The formulation is shown in Table 6.

Table 6: Phase 3/commercial formulation

Component	Role	100-mg % w/w	300-mg % w/w
Core Tablet			
(b) (4)			
Canagliflozin[a]	Active		(b) (4)
Microcrystalline Cellulose	(b) (4)		
Lactose Anhydrous			
Croscarmellose Sodium			
Hydroxypropyl Cellulose			
(b) (4)			
(b) (4)			
Magnesium Stearate[c]			
Filmcoating			
(b) (4)	Yellow		
	White		

[a] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous).

(b) (4)

[c] Vegetable sourced

2.1.3 What is the mechanism of action and therapeutic indication?

Canagliflozin is an inhibitor of SGLT2. The low-affinity/high capacity SGLT2 transporter in the proximal renal tubule reabsorbs the majority of glucose filtered by the renal glomerulus. Pharmacological inhibition of SGLT2 is expected to decrease renal glucose re-absorption, and thereby increase urinary glucose excretion and lower plasma glucose in patients with type 2 diabetes.

In vitro pharmacology studies indicate that canagliflozin was a potent and selective inhibitor of SGLT2. Canagliflozin inhibited sodium-dependent 14C-α-methylglucoside uptake with an IC_{50} of 4.2 nM and 663 nM against hSGLT2 and hSGLT1, respectively.

Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2.1.4 What are the proposed dosage and route of administration?

The sponsor's proposed dose of canagliflozin is 100 mg or 300 mg once daily, preferably taken before the first meal of the day.

In addition, the following dosing recommendations are proposed by the sponsor:

- For patients on insulin or an insulin secretagogue (e.g., sulfonylurea), a lower dose of insulin or the insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with canagliflozin.
- Canagliflozin has a diuretic action. In clinical studies of canagliflozin, patients on loop diuretics, patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m2), or patients ≥ 75 years of age had a higher occurrence of adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, or hypotension). Therefore, in these patients, a starting dose of 100 mg once daily should be considered.
- In patients with evidence of volume depletion, consideration should be given to correcting this condition prior to initiation of canagliflozin.
- In patients started on canagliflozin 100 mg who need additional glycemic control and are adequately tolerating canagliflozin, a dosage of canagliflozin 300 mg is appropriate.

2.1.5 Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?

The to-be-marketed canagliflozin formulation has been used in the pivotal Phase 3 trials. Therefore, no pivotal bioequivalence study was conducted. OSI inspection was not requested for any clinical pharmacology study in this application.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Early Phase 1 clinical pharmacology studies in healthy and T2DM subjects evaluated a wide range of canagliflozin doses (10 mg to 800 mg) to establish the PK, PD, safety and tolerability. Doses of 1200 mg and 1600 mg were evaluated to support dosing in a thorough QT (TQT) trial. Based on the Phase 1 trials, doses ranging from 50 to 600 mg QD doses were tested in the dose-ranging study in T2DM subjects. Based on the data from the Phase 2 study DIA2001, the canagliflozin dose of 100 mg QD and 300 mg QD were selected for pivotal Phase 3 trials.

Once daily and twice daily dosing regimen was also evaluated to determine any potential differences in PK or PD (DIA1032) based on dosing frequency. Most of the drug-drug interaction (DDI) studies were conducted with the 300 mg QD canagliflozin dose. Four DDI studies were conducted with a lower 100 mg or 200 mg QD canagliflozin dose (metformin, hydrochlorothiazide, oral contraceptive and glyburide). Two of these studies were repeated with the 300 mg canagliflozin dose (metformin and hydrochlorothiazide). No significant interaction is expected with the 300 mg dose of canagliflozin and oral contraceptive and glyburide based on observations from the studies conducted with the 200 mg dose (see Section 2.7 for details). The renal impairment study was conducted with the 200 mg dose since this study was conducted before the dose selection for Phase 3 trials. The effect of renal impairment following administration of 300 mg QD is expected to be similar to that observed following administration of the 200 mg QD dose (see Section 2.5 for details).

In addition, several studies were conducted to evaluate the pharmacodynamic activity of canagliflozin.

A list of the key clinical trials is shown in the Table 7 below:

Table 7: Summary of canagliflozin clinical trials

Type of Study	Number of Studies	Population	Number of Subjects
Phase 1			
Mass-Balance	1 (NAP1006)	Healthy subjects	6
Single-Dose	3 (NAP1001, DIA1001, DIA1015)	Healthy subjects	89 (48+17+24)
Multiple-Dose	3 (NAP1008, DIA1030, DIA1032)	Healthy subjects (healthy obese subjects in NAP1008)	121 (60+27+34)
	3 (NAP1002, DIA1007, DIA1023)	Subjects with T2DM	140 (93+20+27)
PD	1 (DIA1022)	Healthy subjects	24
	2 (DIA1025, DIA1045)	Subjects with T2DM	51 (14+37)
Hepatic Impairment	1 (DIA1013)	Otherwise healthy subjects with mild or moderate hepatic impairment or normal hepatic function	16
Renal Impairment	1 (DIA1003)	Otherwise healthy subjects with mild, moderate, or severe renal impairment, with end-stage renal disease, or with normal renal function	40
Non-Caucasian Subjects	3 (TA-7284-01, TA7284-02, DIA1008)	Japanese subjects (healthy and T2DM) or healthy Indian subjects	96 (30+51 +15)
Drug-Drug Interaction	12 (NAP1004, DIA1002, DIA1004, DIA1006, DIA1009, DIA1014, DIA1016, DIA1028, DIA1029, DIA1031, DIA1034, DIA1048)	Healthy subjects	248 (16+28+ 29+28+22+ 18+13+18+ 14+18+30+ 14)
QT/QTc	1 (DIA1010)	Healthy subjects	58
Photosensitivity	4 (NAP1005, DIA1011, DIA1019, DIA1020)	Healthy subjects	67 (12+25+24+ 6)
Phase 2	1 (DIA2001)	Subjects with T2DM	287
	1 (OBE2001)	Nondiabetic obese subjects	250
Phase 3	3 (DIA3004, DIA3005, DIA3009)	Subjects with T2DM	839 (160+220+459)
Total	40		2,332

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Hemoglobin A1c (HbA1c): The primary efficacy endpoint in the Phase 3 trials was the change in HbA1c from baseline at week 24. The American Diabetes Association (ADA) recommends the use of HbA1c as an indicator of glycemic control.

In addition to HbA1c, other pharmacodynamic endpoints were measured including fasting plasma glucose (FPG), post prandial glucose (PPG) and endpoints based on canagliflozin's mechanism of action as an SGLT2 inhibitor such as urinary glucose excretion (UGE) and the renal threshold for glucose excretion (RTg).

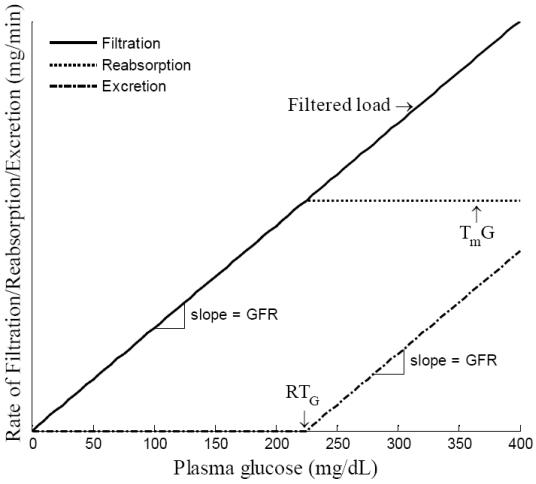
Urinary glucose excretion (UGE): Urinary glucose excretion is easily measured and is a useful marker of PD activity of canagliflozin and in the clinical trials. Urine samples were generally collected over several time intervals during the day in these trials. In most of the studies, UGE analyses used 24-hour cumulative UGE.

The rate of UGE is influenced by factors other than canagliflozin plasma concentrations, including plasma glucose (PG) concentrations and glomerular filtration rate (GFR). As the plasma glucose levels (and to less extent the GFR) is variable in subjects with T2DM, sponsor has proposed the use of a PD measure, RTg, that accounts for the confounding effects of these factors.

Renal threshold for glucose (RTg): RTg was determined by approximating the relationship between UGE and PG by a threshold relationship which was expressed as follows:

$$\text{rate of UGE (mg/min)} = \begin{cases} \text{GFR (dl/min)} \times \left(PG(\text{mg/dl}) - RT_G(\text{mg/dl})\right) & \text{if } PG > RT_G \\ 0 & \text{if } PG \le RT_G \end{cases}$$

This calculation uses the relationship between plasma glucose and the rate of UGE and assumes that there is no UGE when plasma glucose is below RTg and UGE increases linearly with plasma glucose when plasma glucose is above RTg. The relationship is graphically shown in Figure 8 as follows:



Source: Sponsor generated plot
TmG is tubular maximal glucose reabsorption rate

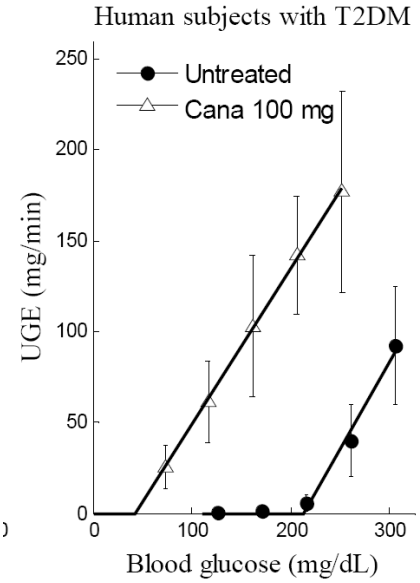
Figure 8: Illustration of idealized threshold relationship between UGE and plasma glucose

In the clinical studies, PG and UGE were measured and GFR was estimated using the MDRD equation, leaving RTg as the only unknown value. While values of RTg are commonly reported to be 180 to 200 mg/dL in normoglycemic subjects, elevated renal glucose reabsorption has been reported in subjects with type 1 and type 2 diabetes, and patients with T2DM have been reported to have minimal glucosuria despite fasting glucose as high as 240 mg/dL.

Because measuring RTg using hyperglycemic clamps generally requires a multiple-step or stepwise hyperglycemic procedure covering a period of 10 or more hours, that method can only be applied in small studies, in specialized laboratories, and is not suitable for routine use in clinical trials. Sponsor developed a new method to calculate RTg during 4-

h mixed meal tolerance test (MMTT) and validated this by comparing the RTg values obtained with their method versus those using the step-wise hyperglycemic clamp approach. Good agreement between the two methods was achieved. Mean RTg values were similar between the MMTT and glucose-clamp methods, with geometric mean ratios (GMRs) of 0.925 in untreated subjects and 1.033 in canagliflozin-treated subjects.

The relationship between mean blood glucose (BG) concentration and UGE rate during the stepwise hyperglycemic glucose clamps is shown in Figure below. Similar to the conceptual relationship mentioned above, the relationship between UGE and PG was described by a threshold relationship. A small amount of UGE is observed until BG concentrations exceeded RTg (Figure 9). When BG concentrations exceed RTg, the rate of UGE increased approximately linearly with increasing BG concentrations. In subjects with T2DM, canagliflozin treatment lowered RTg and shifted the UGE vs. BG relationship to the left, without any meaningful change in the shape of the UGE vs. BG relationship (i.e., no meaningful change in the slope). The RTg values in each group are approximately equal to the x-intercept of the lines relating UGE and PG.



Sponsor study report DIA1025

Figure 9: Urinary glucose excretion at different blood glucose concentrations in untreated and canagliflozin treated T2DM subjects during the stepwise hyperglycemic clamps

2.2.3 Are the active *moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

The active moiety canagliflozin and its metabolites M7 and M5 were appropriately identified and measured in plasma and urine by a validated HPLC-MS/MS assay. Please see Section 2.9 for details regarding bioanalytical methods.

2.3 Exposure-Response

2.3.1 Is there dose-response for effectiveness for canagliflozin?

Yes, the dose-response is evident among 100 mg and 300 mg QD canagliflozin treatment regimens based on efficacy data. The time-profile for the LS mean change from baseline in HbA1c for one of the Phase 3 trial (monotherapy trial DIA3005) is shown in Figure 10 below. A clear separation in mean HbA1c reduction from baseline over time profile was observed between the two active treatment arms (canagliflozin; 100 mg and 300 mg) and the placebo group (Figure 10). At week 26, the placebo adjusted LS Mean change from baseline in HbA1c is numerically higher for the 300 mg QD dose group (-1.16) compared to the 100 mg QD dose group (-0.91) in this trial. The placebo adjusted proportion of subjects who achieved target HbA1c levels of <7.0% by Week 26 was also higher for the 300 mg QD dose group (41.7%) compared to the 100 mg QD dose group (23.9%) in the monotherapy trial. The HbA1c reduction appeared to reach plateau by Week 26. Similar results were evident from the add-on therapy trial (See Appendix, Pharmacometric Review).

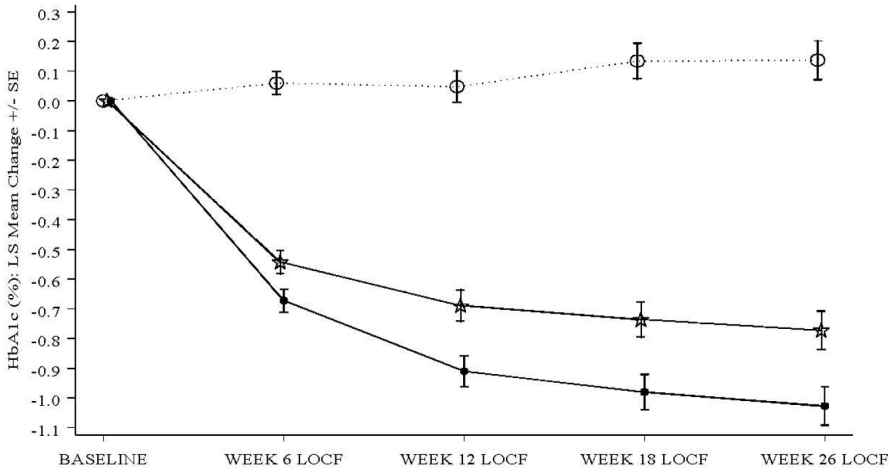


Figure 10: Time-profiles for mean (±SE) change from baseline in HbA1c in Phase 3 monotherapy trial DIA3005

[*Source: Sponsor's Figure 4 in DIA3005 Study Report, Page 85]*

From sponsor's statistical analysis results, there is an evidence of dose-response relationship for effectiveness. The Phase 3 monotherapy and add-on therapy trials demonstrated a dose-dependant decrease in HbA1c, the primary efficacy end-point. (See Appendix, Pharmacometric Review)

Thus based on efficacy data, the dose-response is evident among 100 mg and 300 mg QD canagliflozin treatment regimens with a numerically higher reduction in HbA1c with the 300 mg dose.

2.3.2 Is there an impact of renal impairment on the efficacy of canagliflozin?

Yes, consistent with the mechanism of action, the reduction in HbA1c from baseline in subjects with moderate renal impairment (DIA3004) was of a lower magnitude (approximately half) when compared to the magnitude observed in type 2 diabetic subjects majority with normal renal function or with mild renal impairment in trial DIA3005 or add-on dual therapy trials DIA3006.

Figure 11 below shows the time-profile for the LS mean change from baseline in HbA1c for trial DIA3004. A slight dose-dependent separation in mean HbA1c reduction from baseline over time profile was evident between the two active treatment arms (canagliflozin; 100 mg and 300 mg) and the placebo group (Figure 11). The magnitude of the LS mean change in HbA1c in subjects with moderate renal impairment (DIA3004) was higher than placebo (-0.03) for both 100 mg QD and 300 mg QD dose groups, LS mean HbA1c reduction of -0.33 and -0.44, respectively (See Figure 11). However, the overall magnitude of response was low *per se*, as well as in comparison to the response observed in monotherapy trial DIA3005 (LS mean HbA1c reduction from baseline was -0.77 and -1.03 for 100 mg QD and 300 mg QD, respectively) where majority of subjects were with normal renal function or mild renal impairment shown in Figure 10.

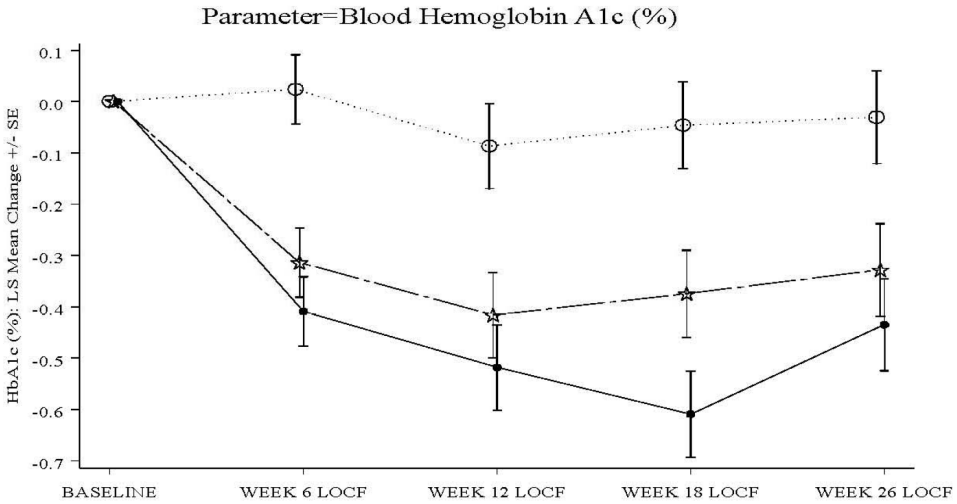


Figure 11: Time-profiles for mean (±SE) change from baseline in HbA1c in moderate renal impairment phase 3 trial DIA3004
[*Source: Sponsor's Figure 4 in DIA3004 Study Report, Page 80]*

Efficacy data was also evaluated based on the baseline renal function for moderate renal impairment trial DIA3004. Figure 12 describes the mean change in HbA1c from baseline to week 26 across treatment groups (placebo, canagliflozin 100 mg and 300 mg) and baseline renal function subcategories (eGFR < 40 and ≥ 40 mL/min/1.73m^2; median baseline eGFR was 40 mL/min/1.73m^2 in each group) in moderate renal impairment trial DIA3004. Overall, in subjects with moderate renal impairment a trend of modest, dose-dependant decrease in HbA1c is observed following 26 weeks treatment with canagliflozin; however, this trend is primarily driven by changes in HbA1c from baseline in subjects with eGFR ≥ 40 mL/min/1.73m^2 (Figure 12).

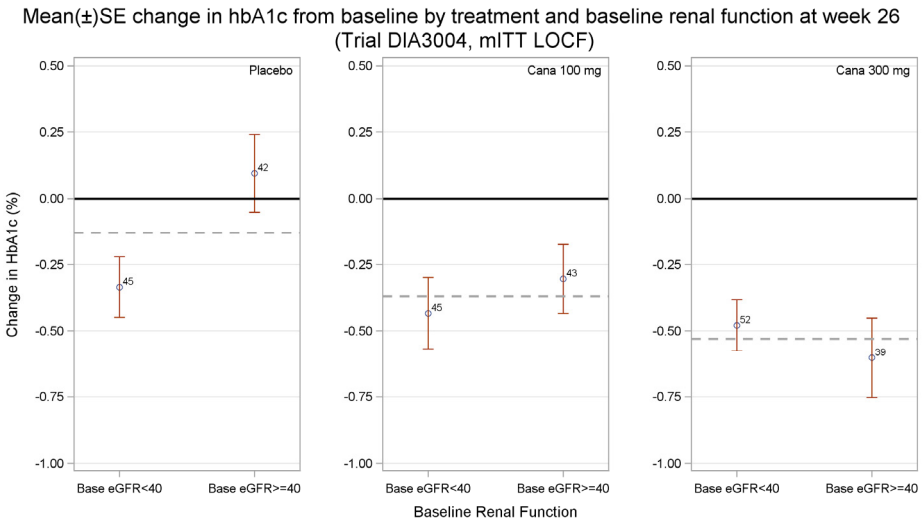


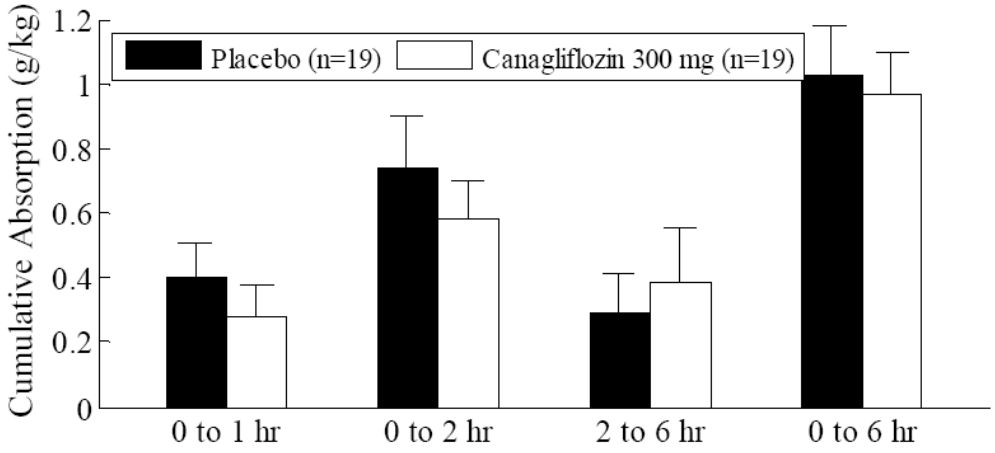
Figure 12: Change in HbA1c is affected by baseline renal function and treatment in type 2 diabetes mellitus subjects with moderate renal impairment (DIA3004)

Overall, consistent with the known mechanism of action of canagliflozin, there appears to be remarkably less reduction in HbA1c levels in type 2 diabetes mellitus subjects with increasing degree of renal impairment. in subjects with moderate renal impairment a trend of modest, dose-dependant decrease in HbA1c is observed following 26 weeks treatment with canagliflozin (Figure 11); however, when evaluated based on baseline renal function this trend is primarily driven by changes in HbA1c from baseline in subjects with eGFR ≥ 40 mL/min/1.73m^2 (Figure 12). Even though the mean response is low in subjects with mild renal impairment compared to subjects with normal renal function, efficacy of canagliflozin is preserved in these patients (See Appendix Pharmacometric Review). However, the magnitude of response is further diminished in moderate renal impairment.

2.3.3 Is there an impact on intestinal glucose absorption by canagliflozin?

It is speculated that after dosing, and during drug absorption, canagliflozin levels within the lumen of the gastrointestinal tract could transiently be high enough to inhibit gastrointestinal SGLT1-mediated glucose absorption and thereby reduce prandial plasma glucose excursions. Sponsor conducted a study, DIA1022 to investigate the effect of canagliflozin (300 mg) on gastrointestinal glucose absorption and metabolism in healthy subjects using a dual-tracer method as compared to placebo. Subjects received after an overnight fast, an intravenous infusion of radio labeled [3-^{3}H]-glucose for approximately 9 hours, about 3 h after which they received a standard Mixed Meal Tolerance Test (MMTT) containing 75 µCi radio-labeled [I-^{14}C]-glucose solution. Canagliflozin/placebo was administered approximately 20 minutes prior to MMTT. With canagliflozin the rate of systemic appearance of orally ingested glucose (a measure of intestinal glucose absorption) was lower for the first 90 minutes compared to placebo and then tended to be

higher over the 2-6 h interval, suggesting a transient inhibition of SGLT1 when given before a meal (Figure 13). By delaying the intestinal glucose absorption, canagliflozin reduced PPG and insulin excursions. The 300-mg dose of canagliflozin also slightly delayed gastric emptying (by approximately 10%) during the first 1 and 2 hours post meal relative to placebo (as determined by plasma acetaminophen concentration time profiles), and the delayed gastric emptying may contribute to the delayed glucose absorption. Due to this action of canagliflozin, sponsor has proposed administering canagliflozin before the first meal of the day to maximize its glucose lowering potential. This is acceptable.



Study Report DIA1022

Figure 13: Mean (+SD) AUCs for Rate of Glucose absorption over 0-1, 0-2, 2-6 and 0-6 hour intervals during MMTT.

2.3.4 What are the characteristics of the dose-response relationships for safety?

The major safety issues associated with canagliflozin were renal safety and volume depletion related adverse events, bone safety issues, genital mycotic infections and cardiovascular safety.

Renal Safety: canagliflozin increases urinary glucose excretion, which leads to an osmotic diuresis. In Phase 1 trials, the increase in urine volume occurred and peaked on Day 1 post-dosing, and attenuated over time. Changes in renal function including increases in serum creatinine and blood urea nitrogen (BUN) were observed in Phase 1 trials with canagliflozin, along with increases in hemoglobin and reductions in systolic and diastolic blood pressure. In Phase 3 trials, subjects were regularly monitored for their renal function and a dedicated efficacy and safety trial has been conducted in subjects with moderate renal impairment with an estimated GFR ranging from 30 mL/min/1,73 m^2 to 50 mL/min/1.73 m^2.

Canagliflozin lowered the eGFR from baseline in both, dose and baseline renal function dependent manner. Effect of canagliflozin on renal function was evaluated based on longitudinal change from baseline in eGFR, and by evaluating the reduction in eGFR as a function of baseline renal function.

Figure 14 shows the longitudinal change from baseline in eGFR by treatment for pooled placebo controlled trials (DS1: Trials DIA3002, DIA3005, DIA3006, and DIA3012). Based on the pooled placebo controlled phase 3 trial data, on average the eGFR decrease from baseline was maximal (approximately -4 and -5 mL/min/1.73m^2, respectively for 100 mg and 300 mg dose of canagliflozin) at the first observation of week 6 after initiation of the treatment. The eGFR values then trended towards improvement but did not return to the baseline by the time of primary end-point assessment at week 26, in most of the trials.

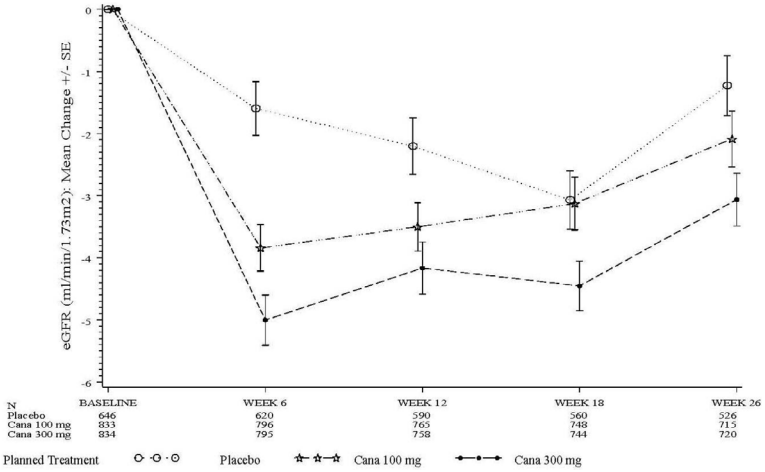


Figure 14: Mean change (+/-SE) in eGFR (mL/min/1.73m2) from baseline over time (ISS Phase 3 Placebo-Controlled Studies Dataset DS1: Safety Analysis Set).
[Source: Summary of Clinical Safety, Figure 17, Page 242]

Figure 15 shows the longitudinal change from baseline in eGFR by treatment for two sensitive specific populations of interest from a safety perspective: subjects with moderate renal impairment in Trial DIA3004 and elderly population in Trial DIA3010. In moderate renal impairment subjects, on average, the eGFR decrease from baseline was maximal (-4.6 and -6.2 mL/min/1.73m^2, respectively for 100 mg and 300 mg dose of canagliflozin) at the first observation of week 3 after initiation of the treatment.

Similar dose dependent decline in renal function was also observed for the trial in elderly subjects (DIA 3010) with eGFR decline of -4.4 and -5.9 mL/min/1.73m^2 at week 6 for 100 mg and 300 mg dose, respectively (Figure 15). As shown in Figure 15, maximum decline in eGFR from baseline was observed at first assessment on Week 3 following treatment with canagliflozin in the moderate renal impaired patients.

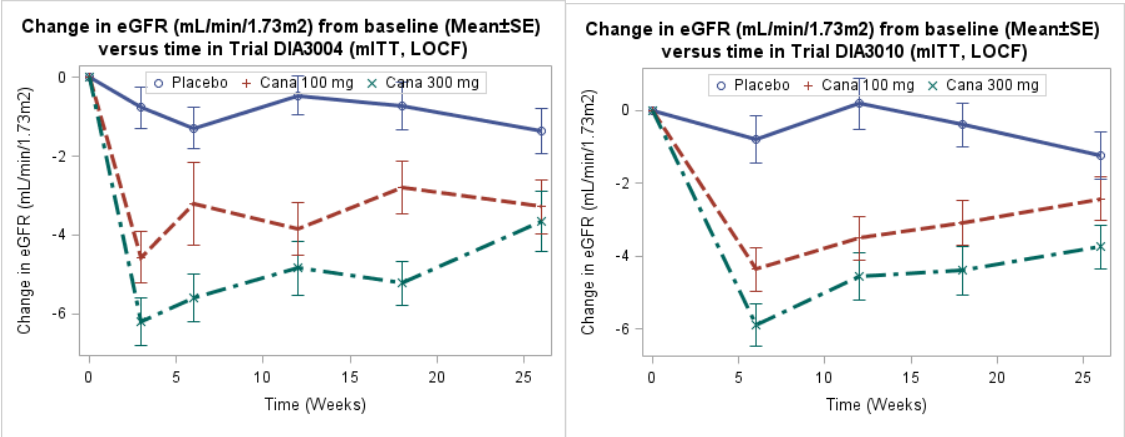


Figure 15: Canagliflozin reduces eGFR from baseline both in type 2 diabetic subjects who have moderate renal impairment (Left), and elderly (Right) type 2 diabetic subjects with normal renal function or mild/moderate renal impairment.

Similar to efficacy, a post-hoc analysis was also conducted to compare the safety in eGFR<40 mL/min/1.73m^2 and eGFR>=40 mL/min/1.73m^2 subgroups.

Change in eGFR in the moderate renal impairment was further evaluated by baseline renal function subgroups (eGFR< 40 and ≥ 40 mL/min/1.73m^2; stratified by median eGFR of 40 mL/min/1.73m^2) at week 3, the point of maximal change in trial DIA3004. Note that, unlike efficacy, which was compared at week 26 between baseline renal function subgroups (Figure 12), the change in eGFR at week 3 or 6 was selected for comparison. Maximum decline in eGFR from baseline was observed at first assessment on Week 3 following treatment with Canagliflozin in DIA3004 trial and at Week 6 for other Phase 3 trials.

In trial DIA3004, a trend of dose-dependent decrease in renal function (i.e., eGFR) was observed for both baseline eGFR< 40 and ≥ 40 mL/min/1.73m^2 subgroups, with relatively higher mean decline in eGFR for 300 mg dose groups than 100 mg dose group. However, on an average, the renal function appeared to recover following longer treatment with Canagliflozin, with relatively low differences for change in eGFR between placebo and treatment groups at week 26. Overall data from trial DIA3004 suggest that mean decline in eGFR was dependent on both dose and baseline eGFR. (See Summary of clinical pharmacology findings and refer Appendix, Pharmacometric Review for details).

Volume depletion related events: As an osmotic diuretic, canagliflozin could also lead to adverse events related to reduced intravascular volume. The incidence of volume depletion-related adverse events was slightly higher in the canagliflozin treatment groups compared to the placebo group, and occurred in 10 (1.2%), 11 (1.3%), and 7 (1.1%) subjects in canagliflozin 100 mg, 300 mg, and placebo groups respectively in the placebo-controlled trials. More subjects in the canagliflozin treatment groups, particularly 300 mg dose group, had volume depletion-related adverse events within the first 30 days of treatment (5 [0.6%] subjects in canagliflozin 300 mg, 2 [0.2%] subjects in

canagliflozin 100 mg, and 1 [0.2%] subject in placebo group. The most common events reported included dehydration, dizziness, hypotension, and syncope. Patients with moderate renal impairment, advanced age, advanced disease stage and on therapies to treat co-morbid conditions (e.g., ACE inhibitors and diuretics) at baseline randomized to canagliflozin appeared to be more susceptible to volume depletion events. The sponsor has proposed a lower starting dose of 100 mg in patients with evidence of volume depletion or in those at a high risk for volume depletion, for example elderly patients and those on loop diuretics (Reference FDA AC background package).

The effect of canagliflozin on some of the key laboratory markers (only those with notable changes such as blood urea nitrogen, hematocrit, and electrolytes - serum magnesium, potassium, phosphate, and sodium) was evaluated from the Phase 3 Trials for DIA3004 and DIA3010 trials to weigh in the risk factors for these two specific populations. There was dose-dependent increase in serum blood urea nitrogen and serum electrolytes (See Appendix, Pharmacometric Review).

The proportion of subjects with adverse events (AEs) related to volume depletion were increased, specifically in the presence of moderate renal impairment, age>=65, and concomitant use of loop diuretics (See Appendix Pharmacometric Review). However, the magnitude of increase in proportion of subjects with volume depletion AEs was higher for canagliflozin in comparison to non-canagliflozin group in presence of these factors.

When evaluated for renal function and use of loop diuretics, the both moderate renal impairment and use of loop diuretics appeared to raise the incidence of volume depletion AE (See Table 8 below) in independent manner with some additive effect when both factors were present. The dose dependent increase in proportion of subjects with AE was seen for all eGFR and loop diuretic use based categories.

Table 8: Proportion of Subjects with Volume Depletion Adverse Events by Use of loop diuretics and renal function - Regardless of Use of Rescue Medication (ISS Phase 3 Broad Dataset: Safety Analysis Set)

		Incidence[a]			
	% (n) in population[b]	Cana 100 mg % (n/N)	Cana 300 mg % (n/N)	Difference % (Cana 300 mg minus Cana 100 mg)	All Non-Cana % (n/N)
eGFR (mL/min/1.73m^2) and Use of Loop Diuretics Category at Baseline	N = 9432				
eGFR ≥60 and No Use of Loop Diuretics	82.5% (n=7784)	1.9% (50/2577)	2.4% (61/2528)	0.5%	1.2% (31/2679)
eGFR <60 and No Use of Loop Diuretics	9.8% (n=927)	4.7% (14/297)	7.2% (22/306)	2.5%	1.9% (6/324)
eGFR ≥60 and Use of Loop Diuretics	4.5% (n=425)	2.3% (3/130)	7.3% (11/151)	5.0%	4.9% (7/144)
eGFR <60 and Use of Loop Diuretics	3.1% (n=296)	4.7% (4/85)	11.1% (11/99)	6.4%	4.5% (5/112)

[a] Incidence of volume depletion adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP.

[b] Number of subjects in the Safety Analysis Set with the baseline characteristic.

Source: Sponsor's Table 90 in Summary of Clinical Safety, Page 247

Bone safety: An increase in trabecular bone volume (hyperosteosis) was observed in rats (refer to pharmacology/toxicology review for nonclinical bone safety details). Due to canagliflozin's mechanism of action, it can potentially affect calcium and phosphorus homeostasis. Fractures as well as bone resorption markers were monitored and collected throughout clinical development. Briefly, canagliflozin appears to cause a dose-dependent small increase in serum phosphorus and magnesium levels and possibly a slight reduction in 1,25-OH vitamin D levels. There was a dose-dependent increase in bone resorption markers, which can contribute to bone fragility and contribute to increase in fractures. Imbalance in upper limb fractures not favoring canagliflozin was also observed (refer to clinical review for details).

Genital mycotic infections: Due to its mechanism of action of increasing urinary glucose excretion, there is a potential to increase fungal growth in the perineum and genitourinary tract. The events occurred in both males and females and canagliflozin was associated with a 4-7 fold increase in the incidence of genital mycotic infections (refer to clinical review for details).

Cardiovascular safety: There were increases in LDL-C following canagliflozin treatment. The range of placebo- or active-control subtracted LS mean percent change in LDL-C from baseline were -2% to 8.5% for canagliflozin 100 mg and 2.8% to 12% for the canagliflozin 300 mg. There was also an increase in non HDL-C levels and HDL-C levels, while triglyceride level reduced. There was an imbalance noted during the first 30 days after randomization in the dedicated cardiovascular outcome trail with higher CV events in the canagliflozin treated group as compared to placebo (refer to clinical and safety statistics review for details).

Photosensitivity: The potential of canagliflozin to have phototoxic effects was investigated due to a signal from nonclinical studies (*in vitro* study in 3T3 fibroblasts and *in vivo* study in rats). 3 studies were conducted to assess the immediate and delayed photosensitivity response. In these studies, the cutaneous photosensitizing potential was measured by the phototoxicity index (PI) as compared to placebo and positive control (ciprofloxacin). Overall, based on these data, the 100 mg and 300 mg once daily dosing regimen was determined to not have a delayed photosensitizing potential (Figures 16 A & B), while the 300 mg bid dosing regimen was considered to be associated with a mild, UVA dependent delayed photosensitization potential (i.e., potential for delayed erythema) that appeared to be less than that observed with ciprofloxacin (Figures 16 A & B). There were some subjects who developed an immediate photosensitivity response in phototesting with standard irradiance (light intensity), that is ~30-fold higher than natural light irradiance. When they were rechallenged at the natural irradiance, the immediate photosensitivity response was eliminated. Therefore, the immediate photosensitivity response observed with testing at the 335±30 nm waveband for the 300 mg dose is irradiance-dependent and is unlikely to be of clinical importance.

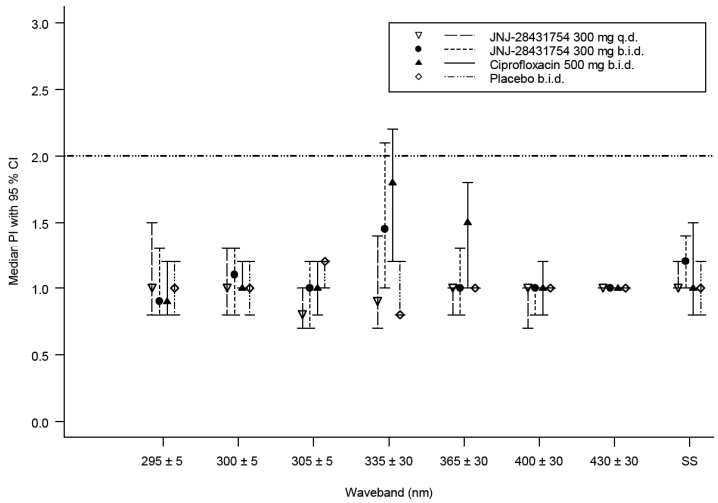
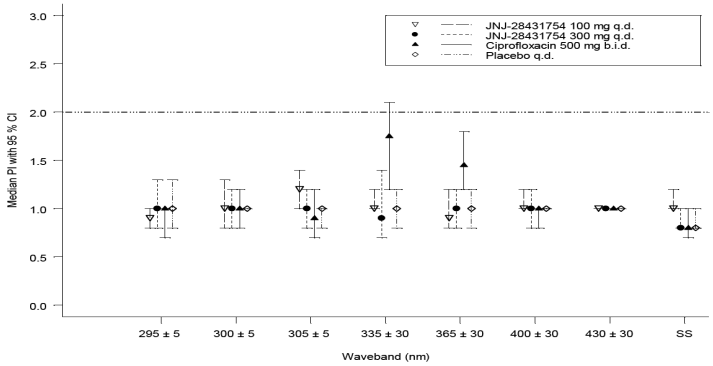


Figure 16 A: Median and 95% Nonparametric Confidence Interval for the Phototoxic Index for Delayed Photosensitivity Response (Delayed Erythema) (Study 28431754DIA1011: Pharmacodynamic Analysis Set)



SS stands for Solar Simulator

Figure 16 B: Median and 95% Non-Parametric Confidence Intervals for the Phototoxicity Index (Study 28431754DIA1019: Pharmacodynamic Analysis Set)

2.3.5 Does this drug prolong QT/QTc Interval?

The sponsor conducted a TQT trial per the ICHE14 guidance. The effect of canagliflozin on the QT/QTC interval was evaluated at the therapeutic dose (300 mg) and at a supra-therapeutic dose (1200 mg) in a randomized, double-blind, placebo and positive-controlled study in 60 healthy subjects. While there was an increase in QTcP (study specific correction method) with moxifloxacin, the positive control, there was no prolongation of the QT/QTc by canagliflozin relative to placebo (Figure 17). The differences in the mean change from baseline in QTcP between canagliflozin and placebo ranged between -2.4 and 0.5 ms for the 300 mg dose group and between -3.9 and -0.7 ms for the 1200 mg canagliflozin group. Further, the upper limits of the 90% CI for the difference in mean QTcP changes from baseline between canagliflozin and placebo were below 10 ms at each time point for each dose group. The results of the trial were

reviewed by the Interdisciplinary Review Team (IRT). A brief summary of the findings are given below. For additional details the reader is referred to the IRT review.

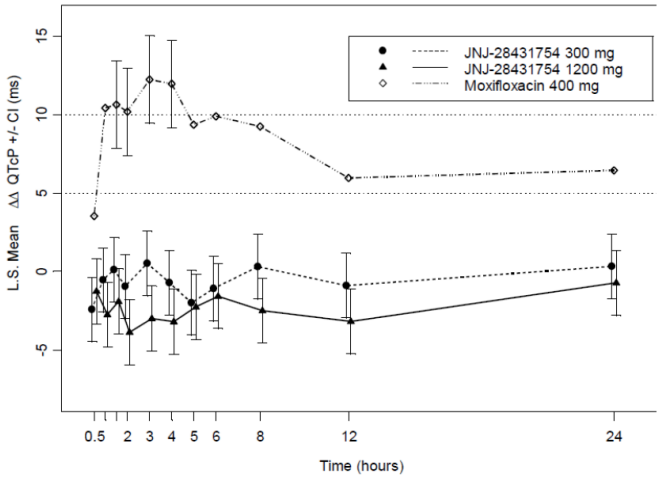


Figure 17: Difference in LS Means QTcP Changes from Baseline between Treatment with 300 or 1,200 mg Canagliflozin or 400 mg Moxifloxacin and Placebo (Study DIA1010)
Source: Study report DIA1010.

2.4 What are the PK characteristics of the drug?

Details on the PK of canagliflozin are discussed below:

2.4.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single dose PK of canagliflozin:
Following single oral doses of 50, 100 and 300 mg, canagliflozin was absorbed with a median Tmax of 1.5 h for all doses. The mean Cmax and AUCinf increased dose-proportionally (Table 9).

Table 9: Pharmacokinetic Parameters of Canagliflozin Following Single-Dose Administration of 50, 100, and 300 mg Canagliflozin in Healthy Subjects (Study DIA1015)

	Mean (SD)		
Parameter	50 mg N=23	100 mg N=24	300 mg N=24
t_{max}, h [a]	1.50 (1.00 - 5.00)	1.50 (1.00 - 5.00)	1.52 (1.00 - 4.98)
C_{max}, ng/mL	551 (137)	1,069 (277)	2,939 (524)
AUC_{∞}, ng.h/mL	3,236 (837)	6,871 (1,751)	20,972 (4,481)
$t_{1/2}$, h	9.4 (1.3)	10.1 (1.9)	11.1 (1.6)
CL/F, L/h	16.3 (3.82)	15.4 (3.96)	15.0 (3.56)
Vd/F, L	218 (37.0)	221 (46.7)	239 (63.7)

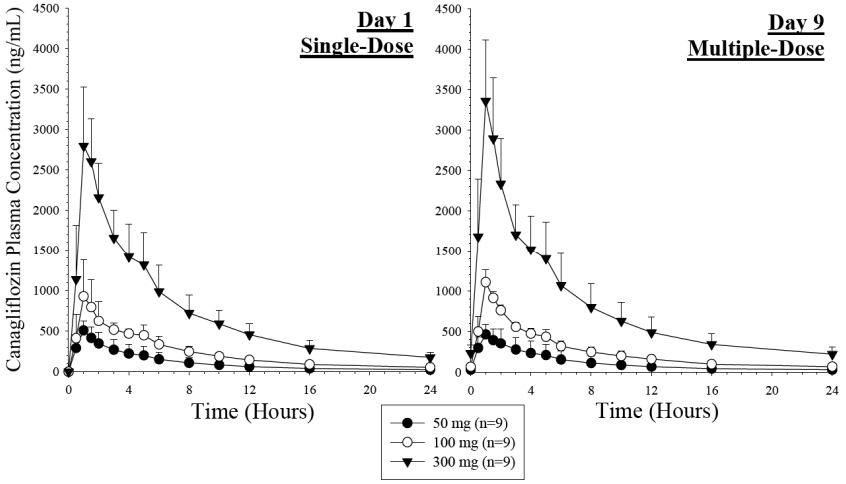
N = maximum number of subjects with data.
[a] Median (range).
Source: DIA1015 study report

In another study where single doses of 800, 1200 and 1600 mg were evaluated, the systemic exposure increased in a dose-dependent manner over this dose-range. The Cmax increased in a dose-dependent manner between the 800 mg and 1200 mg but was similar between the 1200 mg and 1600 mg dose groups.

The PK of metabolites, M5 and M7 were not assessed in these studies.

Multiple-dose PK of canagliflozin:

In study DIA1030, canagliflozin PK following both the single and multiple dosing of 50, 100 and 300 mg was evaluated. Mean plasma Cmax and AUC values of canagliflozin and its metabolites increased in a dose-dependent manner on both Day 1 and Day 9 within this dose-range (Figure 18). The median Tmax was 1 h for all the three dose levels. Mean apparent half-life values ranged from approximately 9-12 h on Day 1 and were 13-14 h on Day 9 and were independent of the doses on both days. Based on the Ctrough values for canagliflozin, and metabolites M5 and M7, steady-state seems to be reached by the 4th QD dose for all the dose groups. No appreciable accumulation was observed at steady-state across the 3 doses with accumulation ratios ranging from 1.03 to 1.12. Across this dose-range, less than 1% of administered canagliflozin dose was recovered unchanged in urine, while the mean percentage of the dose recovered in urine as M7 ranged from 18% to 19% and as M5 ranged from 9% to 10%. The PK parameters of canagliflozin and its metabolites are shown in Tables 10, 11 & 12.



NOTE: Once-daily multiple-dose administration of canagliflozin is from Day 4 to Day 9.

Figure 18: Mean (+SD) Canagliflozin Plasma Concentration-Time Profiles
(Study 28431754DIA1030: Pharmacokinetic Data Analysis Set)

Table 10: Arithmetic mean (SD) canagliflozin PK parameters

(Study 28431754DIA1030: Pharmacokinetic Data Analysis Set)

Day Parameter	50 mg	100 mg	300 mg
Day 1			
N	9	9	9
C_{max} (ng/mL)	521 (132)	1031 (282)	2897 (652)
t_{max} (h)[a]	1.00 (0.98-1.50)	1.02 (1.00-5.00)	1.00 (1.00-1.50)
$AUC_{\tau,sd}$ (ng.h/mL)	2678 (1238)	5519 (565)	17149 (3325)
AUC_{∞} (ng.h/mL)	3087 (1606)	6684 (906)[c]	20732 (4197)
$t_{1/2}$ (h)[b]	9.26 (2.42)	11.7 (2.49)[c]	11.5 (1.16)
CL/F (L/h)	18.6 (5.56)	15.2 (2.05)[c]	14.9 (2.71)
Vd/F (L)[e]	243 (93.7)	254 (50.1)[c]	250 (59.2)
Ae_{0-48} (%,dose)	0.407 (0.215)	0.355 (0.129)	0.408 (0.118)
CL_R (L/h)	0.0757 (0.0484)	0.0564 (0.0208)	0.0616 (0.0114)
Day 9			
N	9	9	9
$C_{max,ss}$ (ng/mL)	494 (164)	1118 (143)	3379 (728)
$t_{max,ss}$ (h)[a]	1.00 (0.50-2.02)	1.00 (1.00-1.50)	1.00 (1.00-1.50)
$AUC_{\tau,ss}$ (ng.h/mL)	2801 (1527)	6056 (959)	19252 (5348)
$t_{1/2}$ (h)[b]	14.0 (4.62)	13.3 (4.79)[d]	13.5 (3.22)
CL_{ss}/F (L/h)	20.6 (6.16)	16.4 (2.16)[d]	16.4 (3.60)
Vd/F (L)[e]	402 (149)	304 (79.7)[d]	319 (104)
Ae_{0-24} (%,dose)	0.544 (0.310)	0.662 (0.214)	0.699 (0.235)
CL_R (L/h)	0.110 (0.0666)	0.111 (0.0359)	0.110 (0.0267)
Acc Ratio	1.03 (0.123)	1.10 (0.119)	1.12 (0.178)

[a] Median (range)

[b] Day 1 based on 72-hour plasma sampling schedule. Day 9 based on 120-hour plasma sampling schedule

[c] n=8 as Subject 01026 (r^2_{adj}: 0.8497) is excluded from the descriptive statistics for parameters estimated based on the terminal phase due to unacceptable variability in the terminal phase.

[d] n=8 as Subject 01006 (r^2_{adj}: 0.8396) is excluded from the descriptive statistics for parameters estimated based on the terminal phase due to unacceptable variability in the terminal phase.

[e] Vd/F = $D/(\lambda_z*AUC_{\infty})$ for single-dose and $D/(\lambda_z*AUC_{\tau,ss})$ after multiple doses

Keys: N = total sample size

NOTE: Once-daily multiple-dose administration of canagliflozin is from Day 4 to Day 9.

Table 11: Arithmetic mean (SD) M7 PK parameters

(Study 28431754DIA1030: Pharmacokinetic Data Analysis Set)

Day Parameter	50 mg	100 mg	300 mg
Day 1			
N	9	9	9
C_{max} (ng/mL)	345 (84.7)	655 (300)	1830 (586)
t_{max} (h)[a]	2.00 (1.45-3.03)	2.00 (1.50-6.00)	2.00 (1.50-3.00)
$AUC_{\tau,sd}$ (ng.h/mL)	2214 (641)	4327 (1465)	14216 (5595)
AUC_{∞} (ng.h/mL)	2376 (769)	5221 (1738)[d]	17743 (7052)
$t_{1/2}$ (h)[b]	8.93 (2.82)	11.7 (2.08)[d]	11.9 (1.29)
Ae_{0-48} (%,dose)	15.9 (3.50)	17.6 (2.72)	16.3 (3.14)
CL_R (L/h)	4.56 (1.07)	5.14 (1.30)	4.49 (1.51)
M/P C_{max} Ratio	0.498 (0.127)	0.462 (0.124)	0.474 (0.160)
M/P AUC_{τ} Ratio	0.649 (0.201)	0.571 (0.177)	0.604 (0.188)
Day 9			
N	9	9	9
$C_{max,ss}$ (ng/mL)	364 (101)	641 (211)	2277 (762)
$t_{max,ss}$ (h)[a]	1.53 (1.50-3.00)	1.50 (1.48-2.00)	2.00 (1.50-2.00)
$AUC_{\tau,ss}$ (ng.h/mL)	2335 (682)	4507 (1354)	16066 (6832)
$t_{1/2}$ (h)[b]	13.7 (5.11)[c]	13.6 (4.93)[e]	14.4 (4.22)
Ae_{0-24} (%,dose)	17.7 (3.97)	19.1 (4.26)	19.4 (3.64)
CL_R (L/h)	5.44 (1.68)	6.32 (2.63)	5.47 (1.64)
M/P C_{max} Ratio	0.572 (0.183)	0.420 (0.121)	0.494 (0.124)
M/P AUC_{τ} Ratio	0.672 (0.230)	0.546 (0.161)	0.608 (0.175)
Acc Ratio	1.06 (0.126)	1.05 (0.121)	1.14 (0.193)

[a] Median (range)

[b] Day 1 based on 72-hour plasma sampling schedule. Day 9 based on 120-hour plasma sampling schedule.

[c] n=8 as Subject 01003 (r^2_{adj}: 0.8811) is excluded from the descriptive statistics for parameters estimated based on the terminal phase due to unacceptable variability in the terminal phase.

[d] n=8 as Subject 01026 (r^2_{adj}: 0.8711) is excluded from the descriptive statistics for parameters estimated based on the terminal phase due to unacceptable variability in the terminal phase.

[e] n=8 as Subject 01006 (r^2_{adj}: 0.8766) is excluded from the descriptive statistics for parameters estimated based on the terminal phase due to unacceptable variability in the terminal phase.

Key: N = total sample size

NOTE: Once-daily multiple-dose administration of canagliflozin is from Day 4 to Day 9.

Table 12: Arithmetic mean (SD) M5 PK parameters

(Study 28431754DIA1030: Pharmacokinetic Data Analysis Set)

Day Parameter	50 mg	100 mg	300 mg
Day 1			
N	9	9	9
C_{max} (ng/mL)	217 (94.5)	405 (95.3)	1177 (488)
t_{max} (h)[a]	2.00 (1.45-5.02)	2.02 (1.50-5.00)	2.00 (1.50-4.00)
$AUC_{\tau,sd}$ (ng.h/mL)	1772 (972)	3412 (944)	10948 (4608)
AUC_{∞} (ng.h/mL)	2235 (1320)[c]	4464 (1518)	14307 (5829)
$t_{1/2}$ (h)[b]	10.0 (2.28)[c]	12.3 (2.92)	12.0 (1.66)
Ae_{0-48} (%dose)	7.99 (3.91)	8.22 (1.84)	8.69 (2.86)
CL_R (L/h)	2.76 (0.705)	2.80 (0.572)	2.83 (0.791)
M/P C_{max} Ratio	0.298 (0.0972)	0.304 (0.108)	0.306 (0.128)
M/P AUC_{τ} Ratio	0.484 (0.197)	0.451 (0.117)	0.467 (0.178)
Day 9			
N	9	9	9
$C_{max,ss}$ (ng/mL)	227 (110)	385 (77.7)	1342 (443)
$t_{max,ss}$ (h)[a]	2.00 (1.50-4.00)	2.00 (1.48-4.00)	2.00 (1.50-4.00)
$AUC_{\tau,ss}$ (ng.h/mL)	1860 (1028)	3512 (1089)	11792 (4332)
$t_{1/2}$ (h)[b]	13.0 (4.50)[d]	14.2 (5.45)	14.3 (4.18)
Ae_{0-24} (%dose)	9.14 (4.05)	8.88 (1.57)	10.0 (2.24)
CL_R (L/h)	3.54 (1.04)	3.69 (1.12)	3.71 (0.844)
M/P C_{max} Ratio	0.345 (0.155)	0.255 (0.0598)	0.297 (0.0877)
M/P AUC_{τ} Ratio	0.513 (0.257)	0.420 (0.0933)	0.447 (0.117)
Acc Ratio	1.07 (0.130)	1.02 (0.0964)	1.11 (0.205)

[a] Median (range)

[b] Day 1 based on 72-hour plasma sampling schedule. Day 9 based on 120-hour plasma sampling schedule.

[c] n=8 as Subject 01009 (r^2_{adj}: 0.8177) is excluded from the descriptive statistics for parameters estimated based on the terminal phase due to unacceptable variability in the terminal phase.

[d] n=6 as Subject 01003 (r^2_{adj}: 0.5870), Subject 1005 (r^2_{adj}: 0.8359), and Subject 1011 (r^2_{adj}: 0.8438) are excluded from the descriptive statistics for parameters estimated based on the terminal phase due to unacceptable variability in the terminal phase.

Key: N = total sample size

NOTE: Once-daily multiple-dose administration of canagliflozin is from Day 4 to Day 9.

2.4.2 ***How does the PK of canagliflozin in T2DM patients compare to that in healthy volunteers?***

Overall, canagliflozin PK profile was similar in T2DM patients as compared to healthy subjects.

In study DIA1023 conducted in T2DM patients, mean plasma canagliflozin concentrations increased at all 3 dose levels (50, 100 and 300 mg) with a median Tmax value of 1.5-2.0 h on Day 1 and Day 7. Mean Cmax and AUC values for canagliflozin on both days increased in a dose dependent manner. Mean apparent t1/2 values ranged from 14 to 16 hours on Day 7 and appeared to be independent of the dose. Accumulation was assessed by the ratio of AUCτ on Day 7 to Day 1 (Table 13). Minimal accumulation of canagliflozin was observed at steady-state across the 3 doses with accumulation ratios ranging from 1.29 to 1.36. Less than 1% of the administered dose was excreted into urine as canagliflozin during a dosing interval at steady state. After repeated doses of canagliflozin, trough concentrations appeared to have achieved steady state by Day 4 for all dose groups.

Canagliflozin metabolites, M7 and M5 plasma concentrations also increased with dose across the dose levels. Across the dose range studies, approximately 27% to 32% of the administered dose was recovered as M7, and approximately 10% of the administered dose was recovered as M5 in the urine in 24 hours at steady-state (Table 14).

Table 13: Mean (SD) Canagliflozin Pharmacokinetic Parameters Following Single and Multiple Oral Doses of 50, 100, and 300 mg Canagliflozin to T2DM Subjects (Study 28431754DIA1023: Pharmacokinetics Data Analysis Set)

	50 mg (n=9)		100 mg (n=8)		300 mg (n=10)	
Parameters	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	426 (106)	536 (174)	1096 (444)	1227 (481)	3480 (844)	4678 (1685)
t_{max} (h)[a]	2.00 (1.00-4.00)	2.00 (1.00-5.00)	1.50 (1.00-5.00)	1.50 (1.00-5.00)	1.5 (1.00-6.00)	1.5 (1.00-2.00)
AUC_τ (ng.h/mL)	3139 (935)	4059 (1105)	6357 (1431)	8225 (1947)	22583 (7343)	30995 (11146)
$t_{1/2}$ (h)	NR	16.3 (4.8)	NR	13.7 (2.1)	NR	14.9 (4.8)
CL_{ss}/F (L/h)	NR	13.2 (3.89)	NR	13.0 (4.43)	NR	11.3 (5.21)
Vd_{ss}/F (L)	NR	301 (90.1)	NR	250 (50.7)	NR	226 (89.4)
Acc Ratio[b]	NR	1.30 (0.108)	NR	1.29 (0.109)	NR	1.36 (0.123)
Ae_{24} (mg)	0.231 (0.0683)	0.417 (0.143)	0.545 (0.101)	0.746 (0.230)	1.21 (0.380)	2.26 (0.968)
Ae_{24} (% Dose)	0.462 (0.137)	0.833 (0.287)	0.545 (0.101)	0.746 (0.230)	0.404 (0.127)	0.752 (0.323)
Ae_{48} (mg)	NR	0.527 (0.194)	NR	0.908 (0.235)	NR	2.85 (1.37)
Ae_{48} (% Dose)	NR	1.05 (0.388)	NR	0.908 (0.235)	NR	0.951 (0.457)
CL_R (L/h)	0.0824 (0.0445)	0.111 (0.0562)	0.0879 (0.0148)	0.0933 (0.0286)	0.0557 (0.0168)	0.0776 (0.0364)

KEY: NR= not reported; n=subsample size; SD=standard deviation
[a] Median (min-max)
[b] Acc Ratio = AUC_τ (Day 7)/AUC_τ (Day 1)

Table 14: Mean (SD) M7 and M5 Pharmacokinetic Parameters on Day 7 following Multiple Oral Doses of 50, 100, and 300 mg Canagliflozin to T2DM Subjects (Study 28431754DIA1023: Pharmacokinetics Data Analysis Set)

M7			
C_{max} (ng/mL)	608 (305)	1276 (588)	3122 (542)
C_{max} (Metabolite/parent Ratios)[b]	0.824 (0.184)	0.800 (0.328)	0.528 (0.154)
t_{max} (h)[a]	3.00 (2.00-5.05)	2.50 (2.00-5.00)	2.00 (1.5-3.00)
AUC_τ (ng.h/mL)	5765 (3989)	10819 (5216)	28110 (7655)
AUC_τ (Metabolite/parent Ratios)[b]	1.00 (0.435)	0.979 (0.468)	0.700 (0.178)
$t_{1/2}$ (h)	17.2 (5.0)	13.9 (2.4)	15.0 (4.7)
Acc Ratio[c]	1.23 (0.146)	1.25 (0.122)	1.28 (0.186)
Ae_{24} (% Dose)	30.7 (6.97)	31.9 (11.0)	27.0 (4.09)
M5			
C_{max} (ng/mL)	324 (132)	559 (191)	1900 (534)
C_{max} (Metabolite/parent Ratios)[b]	0.469 (0.187)	0.371 (0.199)	0.312 (0.0778)
t_{max} (h)[a]	4.00 (1.50-6.00)	3.00 (1.50-6.00)	1.75 (1.00-4.00)
AUC_τ (ng.h/mL)	3607 (2109)	6003 (1943)	21911 (7865)
AUC_τ (Metabolite/parent Ratios)[b]	0.641 (0.253)	0.535 (0.149)	0.537 (0.149)
$t_{1/2}$ (h)	14.8 (3.9)	14.2 (2.6)	13.8 (4.6)
Acc Ratio[c]	1.25 (0.283)	1.22 (0.242)	1.43 (0.337)
Ae_{24} (% Dose)	10.1 (2.62)	9.57 (2.38)	10.5 (2.03)

[a] Median (min-max)
[b] Metabolite/Parent Ratio = [Parameter(metabolite)/Molecular weight(metabolite)]/[Parameter(parent)/Molecular weight(parent)]; Molecular weights: canagliflozin (454 g/mole); JNJ-41488525 (M7) and JNJ-41980874 (M5) (620.6 g/mole)
[b] Acc. Ratio = AUC_τ (Day 7)/AUC_τ (Day 1)

In the population PK analysis, BMI and eGFR were identified as significant covariates on canagliflozin PK. Therefore differences in body weight and renal function between healthy and T2DM subjects can result in some differences in the Cmax and AUC between these two populations.

2.4.3 What are the characteristics of drug absorption?

The absolute oral bioavailability of canagliflozin was 64.9%.

The increases in Cmax and AUC were dose-proportional for canagliflozin following single oral doses of 50 mg to 300 mg (refer 2.4.8). See the single and multiple dose PK data above and effect of food in section 2.8.3.

2.4.4 What are the characteristics of drug distribution?

Canagliflozin is bound extensively (98.3% - 99.2%) to plasma proteins, predominantly to albumin at therapeutic concentrations. This binding is not affected in renal or hepatic impairment. The plasma protein binding of metabolites M5 and M7 is unknown.

The blood to plasma ratio of total radioactivity was constant over time (0.66 – 0.71) across a 24-hour time period indicating that there was no preferential distribution of canagliflozin and its metabolites towards the blood cells.

After IV infusion of canagliflozin in healthy subjects, the mean volume of distribution (Vss) was 119 L. In healthy subjects and in T2DM patients, the mean apparent volume of distribution based on the terminal elimination phase (Vd/F) of canagliflozin following oral administration was between 183 L and 402 L. These values suggest extensive tissue distribution for canagliflozin and were consistent with what was found in animal tissue distribution studies. The highest concentrations of canagliflozin in these studies were in kidney, renal cortex, liver and Harderian gland.

2.4.5 Does the mass balance study suggest renal or hepatic pathway as the major route of elimination?

The predominant route of excretion of radioactivity was via the feces indicating biliary excretion as the major elimination pathways for total radioactivity. Enterohepatic circulation of canagliflozin appeared to be negligible.

At one week after dosing, the total of urinary and fecal excretion of radioactivity amounted to a mean 92.9% of the administered radioactivity (range: 89.7 to 96.0% of the dose) (Table 15). Excretion was mainly via feces; 55.2±5.09% of the total administered radioactivity was found in the fecal extracts, 4.53±1.77% was found in the fecal residues and 0.62±0.73% was found in the lyophilized feces samples. Overall (over 7 days), a total of 60.4±5.73% of the dose was recovered in feces. Urinary excretion averaged 32.5±5.11% of the administered dose (range: 25.7 to 37.7%) (Table 15).

Table 15.

Mean (SD) Total ^{14}C Urine and Fecal Pharmacokinetic Parameters Following a Single Oral Dose of 188 mg JNJ-28431754 in Study 28431754-NAP-1006
(Pharmacokinetic Analysis Set)

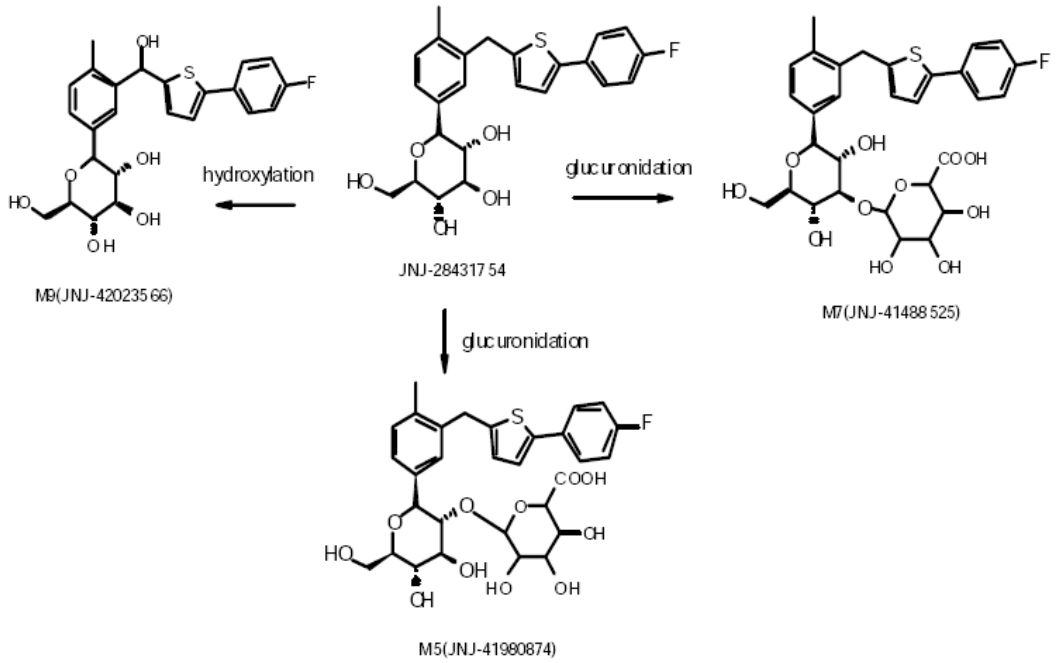
PK Parameters	(n = 6)
Total ^{14}C Urine	
Ae (% dose)	32.5 (5.11)
Total ^{14}C Feces	
Ae (% dose)	60.4 (5.73)

2.4.6 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

The unchanged parent drug is the major drug-related component in plasma and accounted for 45.4% to 98.7% of the total drug-derived components in the radiochromatograms of 0 to 24 hr plasma samples. The remaining drug-derived materials in 1.5 to 12 hour plasma samples were accounted for by two O-glucuronides of unchanged drug (M7 [16.0 to 28.8%] and M5 [1.9 to 29.6%]) and a hydroxylated metabolite M9 (2.42 to 3.70%). No metabolite was detected in the 24th-hour plasma sample.

2.4.7 What are the characteristics of drug metabolism?

The main in vitro metabolic pathway in human hepatocytes was O-glucuronidation of canagliflozin to the O-glucuronide metabolite M7 and a minor O-glucuronide, M5. Additional metabolite formed in human liver microsomes includes the oxygenated metabolite, M9 (Figure 19). All canagliflozin metabolites identified in humans were also found in animal species. Further, in vitro glucuronidation was studied in human liver, kidney and intestinal microsomes and it was determined that M7 was formed both in liver and kidneys while M5 was formed only in the liver microsomes. The enzymes responsible for M7 formation was UGT1A9, and for M5 was UGT2B4. CYP 450 enzymes involvement in canagliflozin metabolism was minimal.



Cross reference: Appendix 2.5

Figure 19: Metabolic pathway of canagliflozin

2.4.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Dose proportionality was estimated using the power model, ($Y = \alpha * Dose^{\beta}$ where Y, α and β correspond to the PK parameter (AUC or Cmax), proportionality constant and an exponent, respectively). If the 90% CI for the exponent β contains 1, the relationship between dose and the PK parameters is considered to be dose proportional.

Dose proportionality was evaluated using canagliflozin (30 mg, 100 mg and 300 mg) AUC and Cmax obtained from the single dose ascending study in fasted healthy subjects (Figure 20). Dose proportionality in this dose range was established since the 90 % confidence intervals for slopes contained 1.

The results slope (90%CI) results for Ln Dose Vs. Ln (AUCinf) or Ln(Cmax) are as follows: AUCinf: 1.04 (0.97 – 1.12)
Cmax: 0.94 (0.87 – 1.01)

Only parent drug was evaluated in this study. Circulating metabolites, M5 and M7 of canagliflozin are pharmacologically inactive and were not evaluated by the sponsor in this study.

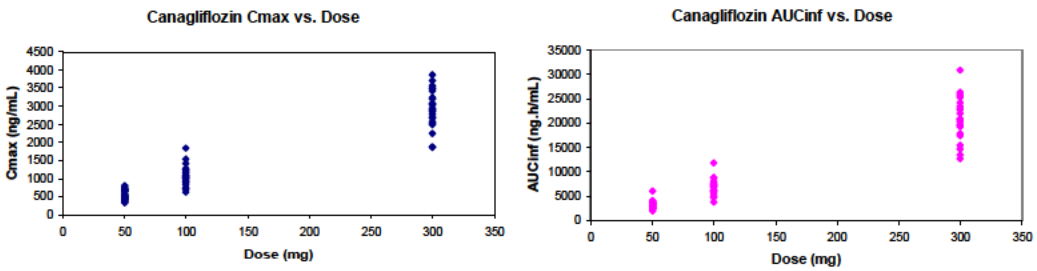


Figure 20: Canagliflozin Cmax and AUCinf following 50, 100 and 300 mg single dose in healthy subjects

2.4.9 How do the PK parameters compare when canagliflozin is administered once daily and twice daily?

Sponsor assessed the steady-state PK and PD following once-daily and twice daily dosing of canagliflozin in healthy subjects in an open-label, multiple-dose study. This study is intended to support the twice-daily dosing regimen of the canagliflozin metformin immediate release fixed dose combination (CANA/MET IR FDC) tablet. The twice-daily dosing regimen is consistent with the dosing and administration recommendations for metformin IR tablets. Four treatments were evaluated, canagliflozin 300 mg once daily for 5 days; canagliflozin 150 mg twice-daily for 5 days; canagliflozin 100 mg once daily for 5 days and canagliflozin 50 mg twice-daily for 5 days.

PK: Mean (SD) plasma canagliflozin pharmacokinetic parameters on Day 5 are shown in Table 13 below. Mean AUC0-24,ss values were similar when comparing the same total daily dose as once- vs. twice-daily (90% CIs for the ratios of the LS means entirely contained within bioequivalence limits of 80% to 125%). Mean apparent t1/2 values ranged from approximately 14 to 15 hours and appeared to be independent of both the dose and dosing regimen (Table 16). Differences in plasma Cmax were observed that were consistent with the expected, i.e., higher Cmax in the morning with the once-daily dose regimens relative to the twice-daily dose administration at the same total daily doses, and higher canagliflozin concentrations at the Cmax of the evening dose with the twice-daily dose administration regimens relative to the canagliflozin concentration at the same time with once-daily dose administration regimens.

Table 16: Arithmetic Mean (SD) Canagliflozin Pharmacokinetic Parameters of Canagliflozin Following Twice-Daily Oral Doses of 50 and 150 mg or Once-Daily Oral Doses of 100 and 300 mg Canagliflozin to Healthy Subjects

(Study 28431754DIA1032: Pharmacokinetic Data Analysis Set)

	50 mg (n=16)	100 mg (n=17)	150 mg (n=16)	300 mg (n=16)
Parameters	Twice-Daily	Once-Daily	Twice-Daily	Once-Daily
$C_{max,ss}$ (ng/mL), morning	568 (125)	943 (239)	1864 (366)	3213 (841)
$C_{max,ss}$ (ng/mL), evening	504 (144)	NA	1764 (349)	NA
$t_{max,ss}$ (h)[a], morning	1.50 (1.00–3.00)	2.00 (1.00–4.00)	1.50 (1.00–4.00)	1.75 (1.00-3.07)
$t_{max,ss}$ (h)[a], evening	1.75 (1.00-4.00)	NA	1.09 (1.02-4.08)	NA
$AUC_{0-12,ss}$ (ng.h/mL)	3254 (589)	NR	11807 (1799)	NR
$AUC_{12-24,ss}$ (ng.h/mL)	2987 (671)	NR	11187 (1813)	NR
$AUC_{0-24,ss}$ (ng.h/mL)	6242 (1252)[b]	6377 (1285)	22973 (3568)[b]	22804 (4650)
$t_{1/2}$ (h)	15.3 (4.45)[c]	14.3 (3.51)	14.1 (1.68)[d]	14.8 (3.79)

KEY: NA- Not applicable; NR= Not reported; n=subsample size; SD=standard deviation

[a] Median (min-max)

[b] For bid dosing regimen, $AUC_{0-24,ss}$ is the sum of $AUC_{0-12,ss}$ and $AUC_{12-24,ss}$

[c] n=14; Subjects 10322 and 103227 excluded due to unacceptable variability in the terminal phase r^2adj.<0.9

[d] n=15; Subject 103208 excluded due to unacceptable variability in the terminal phase r^2adj.<0.9

PD: Renal Threshold for Glucose Excretion (RTG0-24): The LS mean RTG0-24 values for the 300 mg total daily dose were comparable when administered as 150 mg twice-daily or as 300 mg once-daily; similarly, the LS mean RTG0-24 values for the 100 mg total daily dose were comparable when administered as 50 mg twice-daily or as 100 mg once-daily (Table 17).

Table 17: Differences in LS means with associated 90% Confidence Intervals for 24 h mean RTG0-24 of each cohort on Day 5

(Study 28431754DIA1032: Pharmacodynamic Statistical Analyses Set)

	LS Means (mg/dL)			
N	Twice daily (Test)	Once daily (Reference)	Difference in LS Means (90% CI)	Intra-subject CV (%)
		Cohort 1 (300 mg)		
15	51.03	52.49	-1.46 (-4.30; 1.51)	8.8%
		Cohort 2 (100 mg)		
16	59.16	60.27	-1.11 (-2.80; 0.65)	4.7%

Key: CI=confidence interval; CV=coefficient of variation; LS = Least Squares

Note: Data were analyzed on natural log scale, but results were back-transformed to original scale

2.4.10 How do the PK parameters change with time following chronic dosing?

Canagliflozin PK does not change with time following chronic dosing. Accumulation of canagliflozin is predictable from single-dose data and depends on the dosing interval and half-life of the drug. There was no evidence of auto-induction or auto-inhibition of canagliflozin clearance upon multiple dosing. Further, the AUC0-24 across a dose range of 50- 300 mg QD following multiple-dose was similar to AUCinf obtained after single-dose administration in healthy subjects.

2.5 What are the PD characteristics of the drug?

The PD characteristics are discussed below.

2.5.1 *What are the PD characteristics of canagliflozin following single and multiple dose in healthy adults?*

Single dose:

UGE: Following single dose administration of canagliflozin in healthy subjects, the increase in UGE was dose-dependant up to 400 mg dose of canagliflozin given QD. When the dose was increased from 400 mg to 800 mg, no further increase in 24-h UGE was observed, suggesting saturation of UGE response (Table 18). In this study an increase in the rate of UGE occurred up to 7 h after dosing at all doses. After that the UGE rate declined but was higher than placebo over the entire collection interval.

Table 18: Mean (SD) of daily urine glucose excretion in grams in Study NAP1001

Treatment	Time Interval (hours) Postdose				
	Day –1 -24 to 0	Day 1 0 to 24	Day 2 24 to 48	Day 3 48 to 72	Day 4 72 to 96
10 mg, n = 6	0.0750 (0.0334)	8.20 (2.70)	0.697 (1.51)	ND	0.0426 (0.0240)
30 mg, n = 6	0.124 (0.0252)	17.4 (7.40)	0.833 (1.10)	ND	0.0410 (0.0604)
100 mg, n = 6	0.0582 (0.0306)	43.6 (7.09)	12.3 (3.74)	ND	0.177 (0.223)
200 mg, n = 6	0.0462 (0.0265)	48.7 (8.83)	19.3 (9.05)	ND	0.923 (0.668)
400 mg, n = 6	0.0386 (0.0207)	65.0 (12.2)	39.9 (12.7)	ND	5.86 (3.76)
600 mg, n = 6	0.0759 (0.0226)	69.2 (12.2)	47.9 (12.5)	ND	10.2 (4.32)
800 mg, n = 6	0.0729 (0.0357)	65.5 (12.7)	58.0 (16.3)	36.5 (19.9)	19.0 (12.3)
400 mg b.i.d., n = 6	0.0472 (0.0286)	58.9 (8.63)	52.6 (14.4)	40.9 (9.62)	24.5 (8.74)
Placebo, n = 15	0.0803 (0.0546)	0.0598 (0.0274)	0.0479 (0.0425)	0.0640 (0.00232)[a]	0.0549 (0.0497)

[a] n = 3

ND = the 48 to 72 hour urine collection intervals were not determined due to a collection error

Source: Study report NAP1001

RTg: The renal threshold of glucose decreased in a dose-dependent manner with doses up to 100 mg and was almost similar at doses higher than 100 mg (Table 19).

Table 19: Mean (±SE) RTg values following single ascending doses of canagliflozin in Study NAP1001

Treatment/	Renal Threshold (mg/dL)		
Time Interval	0-4 h	4-10 h	10-24 h
10 mg (n=6)	94.9±5.2	94.8±3.6	126.4±10.5
30 mg (n=6)	75.0±2.8	84.8±2.4	116.1±4.4
100 mg (n=6)	57.7±3.3	53.0±4.1	80.6±2.3
200 mg (n=6)	68.3±3.0	62.5±1.5	76.1±2.9
400 mg (n=6)	61.8±3.9	61.1±5.4	72.3±2.7
400 mg bid (n=6)	62.9±3.0	59.5±3.7	63.1±3.5
600 mg (n=6)	58.2±3.6	50.1±3.0	69.2±4.0
800 mg (n=6)	60.3±6.7	48.1±4.6	67.7±0.9

Multiple-dose:

UGE: The daily UGE increased in an apparently less than dose-proportional manner following multiple doses of 30 mg to 600 mg. There was only a slight increase in UGE when 300 mg BID was given as compared to 300 mg and 600 mg QD doses. The increases in mean UGE0-24h were maintained over the 14-day dosing period (Table 20). Similar to the single dose studies, the UGE0-24h appeared to saturate around 300 mg dose.

Table 20: Mean (SD) 24-h UGE with multiple dosing of canagliflozin in obese but otherwise healthy subjects

Day	30 mg q.d. n=12	100 mg q.d. n=12	300 mg q.d. n=12	600 mg q.d. n=12	300 mg b.i.d. n=12	Placebo n=20
Day -1	0.24 (0.26)	0.23 (0.55)	0.060 (0.024)	0.053 (0.016)	0.115 (0.127)	0.087 (0.047)
Day 1	3.17 (3.98)	35.5 (10.8)	53.2 (19.4)	64.1 (32.1)	74.2 (10.6)	0.52 (1.45)
Day 7	10.5 (5.98)	32.6 (13.3)	49.8 (27.1)	45.2 (13.5)	65.7 (18.5)	0.077 (0.049)
Day 14	9.15 (4.16)	33.2 (9.72)	47.0 (23.3)	50.4 (13.0)[a]	61.2 (16.1)	0.087 (0.035)
Day 15	1.38 (0.98)	11.3 (8.11)	35.1 (20.2)	39.0 (14.0)[a]	47.7 (19.6)	0.071 (0.049)
Day 16	0.26 (0.31)	4.67 (6.00)	16.1 (20.0)	29.0 (13.1)[a]	34.0 (19.1)	0.051 (0.043)
Day 17	0.17 (0.27)	1.28 (1.94)	6.19 (10.1)	14.8 (13.3)[a]	22.1 (15.8)	0.069 (0.063)

[a] n = 11 Subject 1060 was not dosed on Day 14

Note: placebo dosed on Day –1, first JNJ-28431754 dose on Day 1 and last dose on Day 14

(g) = grams; q.d. = once daily, b.i.d. = twice daily

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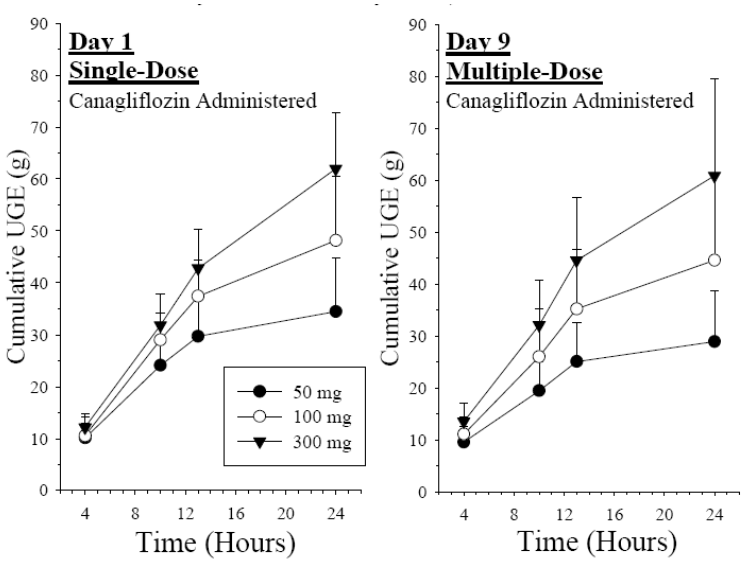
Similarly, in another study (DIA1030), UGE increased in a dose-dependent manner. The UGE profiles on Day 1 and Day 9 were similar. The 50 mg dose had considerably lower UGE in the overnight period than the 100 and 300 mg doses, as evidenced by the flattening of the cumulative UGE curve from 13 to 24 hours (Figure 21). Following the last dose on Day 9, plasma canagliflozin concentrations on Day 10 were decreased and UGE was lower on Day 10 than on Day 1 and Day 9 in all three dose groups.

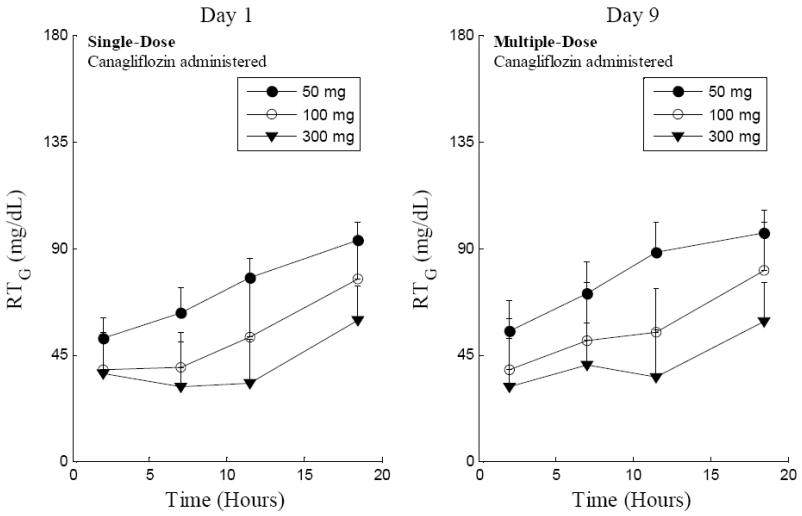


Source: DIA1030 study report

Figure 21: Mean (SD) cumulative UGE-time profiles

RTg: The RTg was lowered in a dose-dependent manner on both Day1 and Day 14 with lowering up to 60 mg/dL following doses of 30 mg to 600 mg over the 14-days dosing period.

In another study, following 50 mg, 100 mg and 300 mg doses of canagliflozin for 9 days, similar dose-dependent decrease in RTg was observed. The 100 mg and 300 mg doses of canagliflozin decreased mean RTg to approximately 38 mg/dL and the 50 mg dose decreased mean RTg to approximately 50 mg/dL. Mean RTg0-24h values decreased in a dose-dependent manner. On Day 9, the 24-hour mean RTg was decreased to approximately 82 mg/dL, 63 mg/dL, and 47 mg/dL after administration of 50-, 100-, and 300-mg canagliflozin, respectively. Mean RTG0-24h values on Day 9 were similar to those on Day 1, at each dose level (Figure 22).



Source: Study report DIA1030

Note: Values of RTg prior to treatment could not be determined in this study because untreated healthy subjects have virtually no UGE following standard meals; The values of RT_g are plotted at the midpoint of the collection interval (eg, $RT_{G0\text{-}4h}$ is plotted at 2-hour).

Figure 22: Mean RTg profiles following single and multiple doses of 50 mg, 100 mg and 300 mg canagliflozin

The PD of canagliflozin administered once daily was similar when compared to twice daily regimen (same total daily dose). See section 2.4.9 above.

2.5.2 How does the PD of canagliflozin in T2DM patients compared to that in healthy volunteers?

The effect of canagliflozin in T2DM patients was similar to those observed in healthy subjects, i.e. increase in UGE and reduction in RTg although the magnitude of the change was different in the two populations.

Treatment with canagliflozin significantly increased UGE relative to baseline (Day-1) and also relative to placebo in a dose-dependent manner. The mean increases in the 24-h UGE from baseline at 100-400 mg once daily and 300 mg twice daily doses were similar, suggesting saturation of the SGLT-2 inhibition (Figure 23).

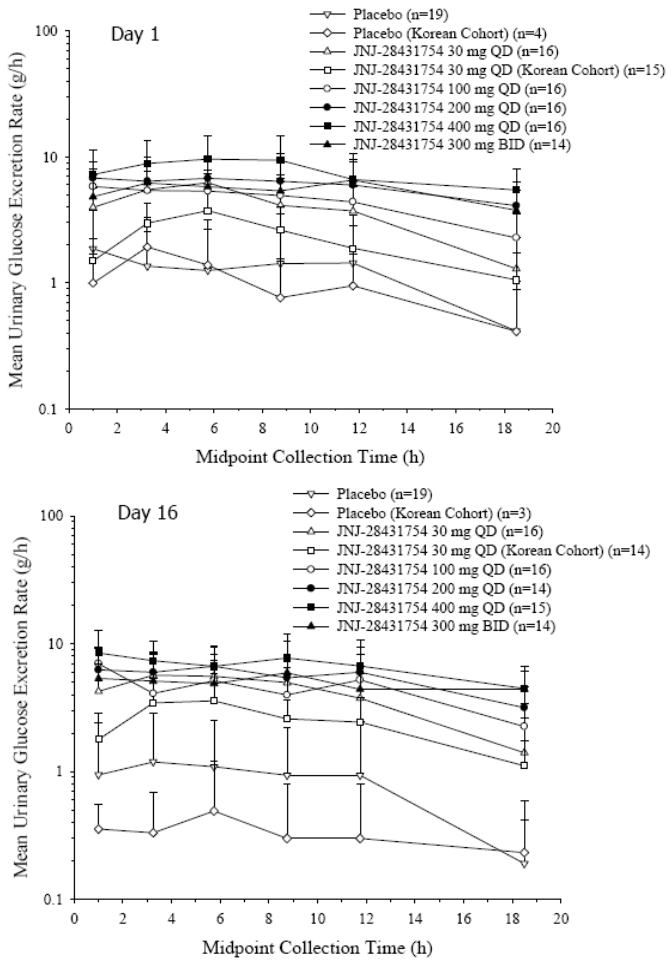


Figure 23: Mean (+SD) Urinary Glucose Excretion (UGE) Rate (g/h) on Day 1, and Day 16 in T2DM patients in Study 28431754-NAP-1002

Results from Day -1 (Table 21) showed that the renal threshold in the diabetic subjects is higher than the commonly reported values of 180 to 200 mg/dL. The mean (±SD) value of RTg on Day -1 was 248 ± 28 mg/dL, with a range from 178 to 325 mg/dL. The values of RTg were generally higher in subjects with higher plasma glucose concentrations. Renal glucose reabsorption capacity in subjects with type 2 diabetes increased with increasing plasma glucose concentrations. All treatment groups lowered RTg by more than 100 mg/dL when compared to the placebo group (Table 21). The 24-h mean RTg was reduced to approximately 70 to 90 mg/dL in the highest dose groups.

Table 21: Mean (SD) Renal Threshold Values at Each Time Interval for Each Treatment in T2DM patients in Study 28431754-NAP-1002

	Day -1			Day 1			Day 16		
Treatment	$R_{T\ 0\text{-}4.5}$	$R_{T4.5\text{-}10.5}$	$R_{T10.5\text{-}24}$	$R_{T\ 0\text{-}4.5}$	$R_{T4.5\text{-}10.5}$	$R_{T10.5\text{-}24}$	$R_{T\ 0\text{-}4.5}$	$R_{T4.5\text{-}10.5}$	$R_{T10.5\text{-}24}$
30 mg	268.7[a]	253.2[b]	248.0[c]	146.1	145.4	171.5	128.0	146.4	165.0
(n=16)	(25.5)	(30.2)	(21.4)	(28.4)	(25.4)	(22.0)	(21.8)	(29.3)	(31.1)
30 mg Korean	247.2	229.1[a]	241.7[d]	174.8	129.8	169.2	119.2[a]	116.8[a]	131.9[a]
(n=15)	(30.2)	(29.7)	(35.7)	(35.7)	(54.3)	(34.3)	(36.9)	(31.2)	(18.6)
100 mg	245.5[c]	247.8[e]	229.5[a]	147.3	127.5	150.1	106.4	110.3	122.5
(n=16)	(26.7)	(28.1)	(33.9)	(31.4)	(19.9)	(21.2)	(30.8)	(22.8)	(14.1)
200 mg	247.5	241.3	238.7[f]	125.6	115.6	116.8	96.5[a]	100.6[a]	102.7[a]
(n=16)	(35.8)	(24.9)	(39.2)	(25.9)	(37.8)	(25.9)	(33.3)	(20.4)	(22.0)
300 mg BID	243.4[f]	239.1[g]	230.0[e]	122.0	111.3	94.3	75.0	81.3	96.6
(n=14)	(34.1)	(38.2)	(35.3)	(27.2)	(27.3)	(26.1)	(23.3)	(29.3)	(16.3)
400 mg	262.3	259.6[c]	248.7[d]	127.0	110.6	113.8	72.9[b]	95.5[b]	94.0[b]
(n=16)	(33.4)	(42.6)	(32.7)	(36.9)	(32.9)	(22.9)	(23.4)	(23.9)	(17.6)
Placebo	245.0[h]	242.8[a]	234.2[a]	244.7[b]	247.1[b]	228.6[a]	236.9[f]	242.6[f]	230.5[d]
(n=19)	(24.3)	(35.3)	(32.4)	(32.6)	(34.1)	(33.8)	(28.4)	(20.9)	(35.7)
Placebo Korean	264.5	251.6	243.9	248.5	259.0	243.8	229.1[i]	215.7[j]	236.5[j]
(n=4)	(34.0)	(44.6)	(22.7)	(28.2)	(40.9)	(27.8)	(14.8)	(21.0)	(17.2)

[a] (n=14), [b] (n=15), [c] (n=13), [d] (n=12), [e] (n=9), [f] (n=11), [g] (n=10), [h] (n=17), [i] (n=3), [j] (n=2)

In another study (DIA1023), the PD following 50 mg, 100 mg and 300 mg QD was investigated in T2DM patients. The 24-hour UGE increased statistically significantly compared to placebo for all canagliflozin doses after single dose as well as after multiple dose administration. Following a single oral dose administration of 50-, 100-, and 300-mg canagliflozin, mean 24-hour UGE increased from Day -1 to Day 1 with mean (SD) increases of 66.2 (12.9), 101.67 (17.9) and 102.5 (23.8) g, respectively. This increase in 24-hour UGE was maintained over the 7-day dosing period, with mean increases ranging from approximately 85 to 103 g by Day 7 (Table 22).

Table 22: 24-Hour Mean UGE Following Single- and Multiple-Dose Administration of 50, 100, and 300 mg qd Canagliflozin in Subjects with T2DM (Study DIA1023)

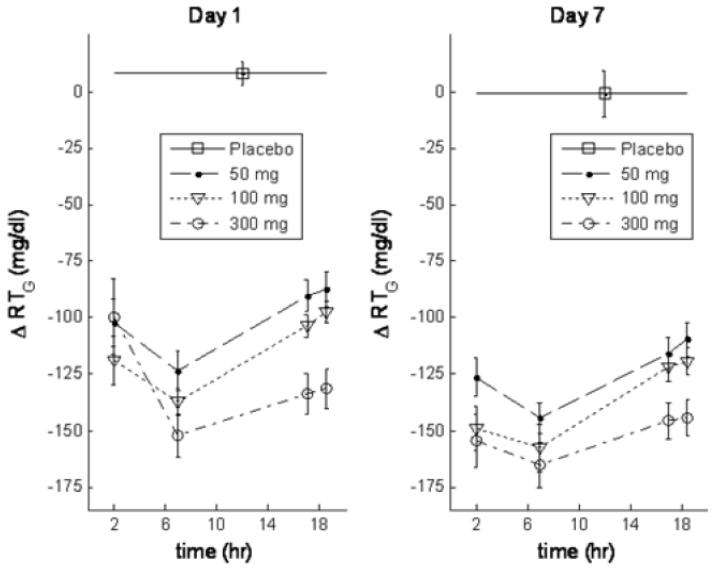
Study Day	Placebo (n=9)	50 mg (n=9)	100 mg (n=8)	300 mg (n=10)
Day -1, Baseline (g)	9.75 (6.594)	14.54 (19.140)	15.63 (12.432)	10.54 (9.236)
Day 1	12.36 (8.631)	80.78 (26.770)	117.30 (18.804)	113.09 (27.222)
Change From Baseline (g)	2.61 (4.762)	66.24 (12.915)	101.67 (17.971)	102.54 (23.882)
Diff of LS Means [SE][a]	NA	62.95 [8.026][b]	98.24 [8.307][b]	99.82 [7.748][b]
90% CI		(49.345;76.563)	(84.155;112.325)	(86.684;112.956)
Day 7	16.16 (13.970)	99.25 (17.539)	119.08 (30.660)	111.50 (24.346)
Change From Baseline (g)	6.41 (14.150)	84.71 (20.937)	103.46 (24.321)	100.95 (21.959)
Diff of LS Means [SE][a]	NA	79.59 [9.830][b]	98.64 [10.174][b]	94.76 [9.488][b]
90% CI		(62.926;96.259)	(81.386;115.886)	(78.669;110.845)

KEY: LS=least squares; NA=not applicable; n=subsample size; SD=standard deviation; SE=standard error

[a] P-values and CIs are based on the pairwise comparison between a dose of canagliflozin and placebo using least squares (LS) means from an ANCOVA model including treatment as a factor and baseline (Day -1) UGE as a covariate. No adjustments for multiplicity have been made.

[b] P-value <0.001

Mean RTg values on Day -1 ranged from approximately 212 to 244 mg/dL and tended to be higher in subjects with higher plasma glucose on Day -1. The renal threshold for glucose excretion was reduced in a dose-dependent manner on both Day 1 and Day (Figure 24). The 100-mg canagliflozin dose provided the maximal lowering of RTg during the middle portion of the day (6-8 h post-dose), with slightly less lowering later in the day and in the overnight period. On the other hand, following the 300-mg canagliflozin dose, the maximum lowering of RTg occurred at 6-8 h which was maintained through 18 h (Figure 24). The 24-hour mean RTg was lowered by >100 mg/dL compared to the Day -1 values in all 3 dose groups, whereas almost no change was observed in the placebo group across the days; the mean percent change in the 24-hour mean RTg (Day 7 values relative to Day -1 values) was 52% in the 50-mg group and 64% in the 100 and 300-mg canagliflozin groups.



Source: Clinical Study Report 28431754DIA1023
Note: RTg values were calculated over the intervals 0-4, 4-10, 10-24, and 13-24 hours after dosing. Values shown are mean ± SE. RTg values are plotted at the midpoint of the time interval during which they are calculated (e.g., the value of RTG calculated over the 0 to 4 hour interval is plotted at t=2 hour). Values for placebo subjects were calculated using the full 24-hour PG and UGE values (because placebo-treated subjects often had insufficient UGE in one of the subintervals to permit RTG to be determined accurately) and hence are the same throughout the day; these points are plotted at t=12 hours.

Figure 24: Intra-Day Time Profile for Change From Baseline in RTG Values on Day 1 (Left) and Day 7 (Right)

2.6 Intrinsic Factors

2.6.1 What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Renal Impairment: In an open-label, single-dose, multicenter, parallel-group study, 40 subjects were assigned to 1 of 5 groups (8 subjects per group) as determined by creatinine clearance (CLCR) based on the Cockroft-Gault equation as follows:
• Group 1: 8 subjects with normal renal function and no evidence of kidney damage (CLCR ≥80 mL/min)
• Group 2: 8 subjects with mild renal impairment (CLCR 50 to <80 mL/min)
• Group 3: 8 subjects with moderate renal impairment (CLCR 30 to <50 mL/min)
• Group 4: 8 subjects with severe renal impairment (CLCR <30 mL/min)
• Group 5: 8 subjects with ESRD (requiring HD for at least 3 months before screening; CLCR was not calculated)
Subjects in Groups 1 to 4 received 1 treatment (a single 200 mg dose) of canagliflozin. Subjects in Group 5 received 1 treatment sequence consisting of a single oral dose (Treatment A, post-dialysis) of canagliflozin followed by a second single oral dose (Treatment B, pre-dialysis) approximately 10 days later.

The sponsor amended the original study report with reanalysis of the data after classifying the subjects into renal function groups based on eGFR (MDRD equation) as recommended by the 2010 FDA draft guidance. The new renal function groups were:

- Normal renal function (eGFR ≥ 90 mL/min/1.73m^2)
- Mild renal impairment (eGFR 60 to 89 mL/min/1.73m^2)
- Moderate renal impairment (eGFR 30 to 59 mL/min/1.73m^2)
- Severe renal impairment (eGFR 15 to 29 mL/min/1.73m^2)
- End Stage Renal Disease (ESRD) (< 15 mL/min/1.73m^2 not on dialysis, or subjects requiring dialysis)

This resulted in a change in the renal function category for some of the subjects and resulting in N= 3 for normal, N= 10 for mild, N= 9 for moderate and N= 10 for severe renal impairment, respectively. The PK and PD results from the analysis of eGFR using MDRD equation were generally consistent with what was observed for Cockroft-Gault estimates of creatinine clearance.

Canagliflozin PK: The mean canagliflozin half-life (t1/2) was slightly longer in the groups of subjects with mild, moderate, and severe renal impairment (22.8, 17.5, and 23.9 hours, respectively) and ESRD subjects (pre-dialysis group, [21.4 hours], post-dialysis group [17.2 hours]), when compared to the normal renal function group (14.2 hours). Mean apparent oral clearance (CL/F) values for canagliflozin were lower in subjects with mild (↓14%), moderate (↓25%) and severe (↓36%) renal impairment compared to normal subjects (Table 23).

As compared to the normal renal function group, the geometric mean canagliflozin AUC_{inf} values were about 15%, 29% and 53% higher in subjects with mild, moderate and severe renal impairment groups, respectively (Figure 25). The exposure in ESRD subjects was comparable to normal group. On the other hand, mean canagliflozin C_{max} values in all the renal impairment categories were lower than in the normal group (Table 23).

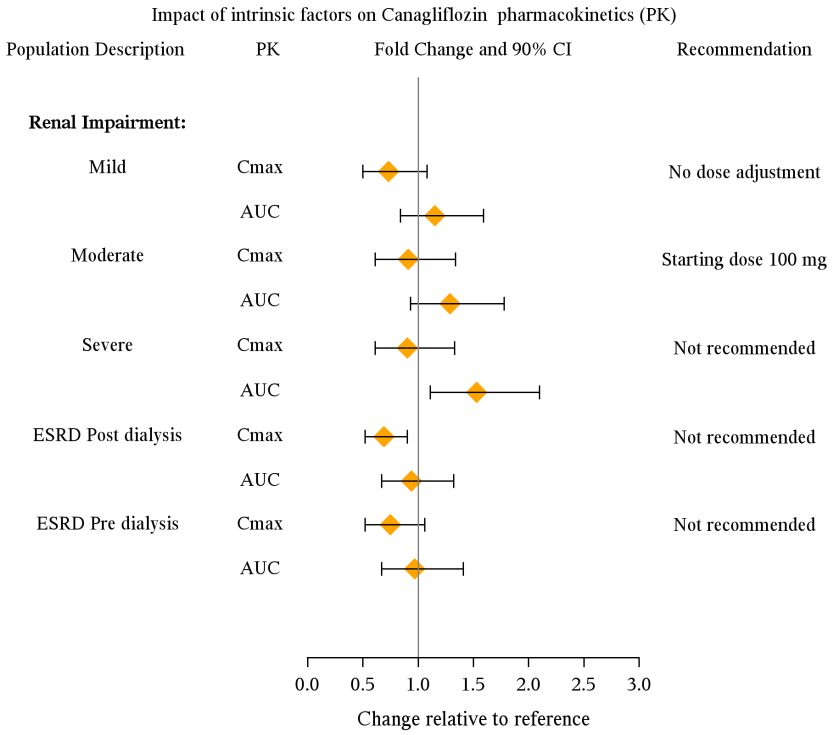


Figure 25: Effect of renal impairment on canagliflozin pharmacokinetics. ***Dashed line indicate the 80%-125% limit***

Table 23: Arithmetic mean (SD) canagliflozin plasma and urine PK parameters in subjects with varying degrees of renal function. (Source: Sponsor's study DIA1003 addendum).

PK Parameters	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impaired	Severe Renal Impairment	ESRD Pre-Dialysis[b]	ESRD Post-Dialysis[b]
N	3	10	9	10	8	8
C_{max} (ng/mL)	1880 (475)	1469 (669)	1717 (427)	1746 (665)	1433 (509)	1287 (277)
t_{max} (h)[a]	1.00 (0.50-2.00)	3.50 (1.00-5.00)	1.50 (1.00-5.00)	1.50 (1.00-5.00)	2.25 (1.0-6.0)	2.00 (1.5-5.0)
AUC_{∞} (ng.h/mL)	14862 (5380)	17172 (6075)	18715 (4504)	22304 (5566)	14205 (3648)	13587 (3216)
AUC_{last} (ng.h/mL)	14663 (5369)	16821 (6063)	18440 (4395)	21790 (5494)	13758 (3322)	13271 (3019)
$t_{1/2}$ (h)	14.2 (5.21)	22.8 (9.34)	17.5 (6.11)	23.9 (10.6)	21.4 (12.0)	17.2 (4.9)
Vd/F (L)	277 (23.7)	427 (205)	279 (94.2)	322 (148)	428 (205)	365 (68.8)
CL/F (L/h)	14.9 (6.12)	12.8 (3.78)	11.2 (2.56)	9.51 (2.46)	15.0 (4.05)	15.4 (3.22)
Ae (% dose)	0.74 (0.37)	0.40 (0.13)	0.32 (0.16)	0.19 (0.09)	NA	NA
CL_R (L/h)	0.13 (0.11)	0.05 (0.03)	0.04 (0.02)	0.02 (0.01)	NA	NA

[a] Median (range)
[b] Pre-dialysis (dosed 2 hours before HD) or post-dialysis (1 hour after HD)
[c] N=7
Note: eGFR ranges for each renal function group are as follows: Normal = ≥ 90 mL/min/1.73m^2; Mild = 60-89 mL/min/1.73m^2; Moderate = 30-59 mL/min/1.73m^2: Severe = 15-29 mL/min/1.73m^2
Key: N=total number of subjects; SD=standard deviation; ESRD: End Stage Renal Disease

Canagliflozin metabolites M7 and M5 PK:
Mean M7 AUC_{inf} was approximately 3%, 127%, 71%, 69% and 64% higher in groups of subjects with mild, moderate and severe impairment and in ESRD subjects (pre-dialysis and post-dialysis), respectively, when compared to the normal renal function group. While, the mean M7 C_{max} was approximately 18% lower and 91%, 14%, 39% and 27% higher in the groups of subjects with mild, moderate and severe renal impairment and in ESRD subjects (pre-dialysis and post-dialysis), respectively, when compared to the normal renal function group (Table 24).

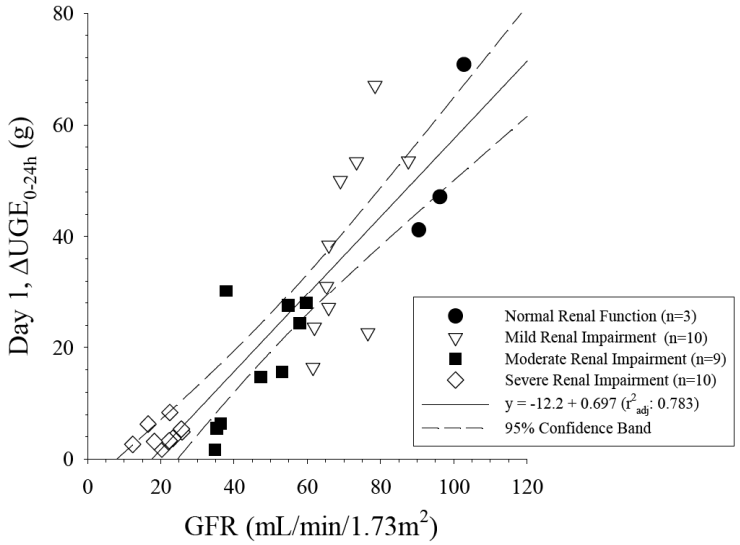
Mean M5 AUC_{inf} was approximately 31%, 172%, 195%, 160% and 190% higher in groups of subjects with mild, moderate and severe impairment and in ESRD subjects (pre-dialysis and post-dialysis), respectively, when compared to the normal renal function group. The mean M5 C_{max} was approximately 3% lower and 102%, 61%, 100% and 117% higher in the groups of subjects with mild, moderate and severe renal impairment, and in ESRD subjects (pre-dialysis and post-dialysis), respectively, when compared to the normal renal function group (Table 24).

Table 24: Arithmetic mean (SD) M7 and M5 plasma and urine PK parameters in subjects with varying degrees of renal function. (Source: Sponsor's study DIA1003 addendum).

Parameters	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impaired	Severe Renal Impairment	ESRD Pre-Dialysis[a]	ESRD Post-Dialysis[a]
M7						
N	3	10	9	10	8	8
C_{max} (ng/mL)	1420 (60.0)	1255 (482)	3038 (146)	1699 (530)	2313(1372)	2038 (1197)
t_{max} (h)[a]	2.00 (2.00-3.00)	4.00 (2.00-6.00)	4.00 (2.00-6.00)	3.00 (2.00-6.00)	3.52 (2.00-6.00)	3.00 (2.00-6.00)
AUC_{∞} (ng.h/mL)	16887 (4988)	17669 (5901)	46522 (36263)	30780 (14454)	35120 (29380)	32229 (25524)
AUC_{last} (ng.h/mL)	15726 (5579)	17257 (5842)	46169 (36180)	29983 (14389)	34111 (27895)	31744 (25079)
$t_{1/2}$ (h)	22.0 (17.6)	21.6 (8.92)	16.9 (4.19)	24.8 (14.53)	22.5 (12.8)	17.9 (7.1)
C_{max} Molar Ratios[b]	0.584 (0.189)	0.677 (0.249)	1.34 (0.616)	0.746 (0.231)	1.20 (0.61)	1.22 (0.08)
AUC_{∞} Molar Ratios[b]	0.848 (0.104)	0.785 (0.219)	1.79 (1.02)	1.00 (0.349)	1.84 (1.42)	1.79 (1.31)
Ae (% dose)[c]	16.1 (5.03)	16.1 (3.87)	11.8 (3.72)	4.20 (1.82)	NAs	NAs
M5						
N	3	10	9	10	8	8
C_{max} (ng/mL)	749 (85.0)	746 (172)	1688 (939)	1357 (714)	1628 (689)	1725 (687)
t_{max} (h)[a]	4.00 (4.00-4.00)	4.50 (2.00-8.00)	4.02 (2.00-6.00)	4.00 (4.00-24.12)	6.00 (6.00-6.00)	6.00 (5.00-6.00)
AUC_{∞} (ng.h/mL)	10826 (4896)	14176 (4871)	33932 (28767)	36437 (23912)	32238 (22600)	33625 (19683)
AUC_{last} (ng.h/mL)	12389 (4546)	13886 (4901)	33648 (28759)	35669 (23724)	31198 (21422)	32975 (19106)
$t_{1/2}$ (h)	9.72 (1.10)	20.8 (10.2)	17.2 (4.59)	22.1 (8.52)	19.4 (9.7)	16.9 (6.2)
C_{max} Molar Ratios[b]	0.310 (0.117)	0.415 (0.147)	0.711 (0.321)	0.586 (0.287)	0.87 (0.39)	1.04 (0.50)
AUC_{∞} Molar Ratios[b]	0.630 (0.061)	0.636 (0.239)	1.25 (0.759)	1.15 (0.600)	1.65 (1.07)	1.84 (0.96)
Ae (% dose)[c]	7.14 (1.96)	7.43 (2.75)	7.91 (3.49)	2.28 (1.29)	NAs	NAs

[a] Median (Range)
[b] Molar Ratio = [Parameter(metabolite)/Molecular weight(metabolite)]/[Parameter(parent)/Molecular weight(parent)]; Molecular weights: canagliflozin (454 g/mole); JNJ-41488525 (M7)and JNJ-41980874 (M5) (620.6 g/mole)
[c] Ae (% dose) adjusted for molecular weight
[d] Pre-dialysis (dosed 2 hours before HD) or post-dialysis (1 hour after HD)
Note: eGFR ranges for each renal function group are as follows: Normal = ≥ 90 mL/min/1.73m^2; Mild = 60-89 mL/min/1.73m^2; Moderate = 30-59 mL/min/1.73m^2: Severe = 15-29 mL/min/1.73m^2
Key: N=total number of subjects; SD=standard deviations; ESRD: End Stage Renal Disease; NAs=Not Assessable

Urinary Glucose Excretion (UGE) Following Canagliflozin: Across all renal function groups, canagliflozin treatment increased UGE0-24h relative to baseline. The extent of the increase in UGE0-24h from baseline increased with increasing GFR (Figure 26).



Note: $\Delta UGE_{0\text{-}24h}$ defined as the difference in UGE on Day 1 from Day -1.
Note: eGFR ranges for each renal function group are as follows: Normal = ≥ 90 mL/min/1.73m^2; Mild = 60-89 mL/min/1.73m^2; Moderate = 30-59 mL/min/1.73m^2: Severe = 15-29 mL/min/1.73m^2

Figure 26: Change in urinary glucose excretion from baseline on Day 1 versus GFR

Renal Threshold for Glucose Excretion (RTG): In subjects with normal renal function and mild renal impairment, the 24-hour mean RTG was approximately 76 mg/dL and 72 mg/dL, respectively, after administration of canagliflozin, whereas in subjects with moderate or severe renal impairment, the 24-hour mean RTG was approximately 86 mg/dL and 96 mg/dL with treatment, respectively (Table 25).

Table 25: Renal threshold for glucose excretion in different degrees of renal function

Renal Function	$RT_{G0\text{-}4h}$ (mg/dL)	$RT_{G4\text{-}10h}$ (mg/dL)	$RT_{G10\text{-}24h}$ (mg/dL)	24-hour Mean RT_G (mg/dL)
Normal (n=3)	74.4 (3.33)	70.9 (13.2)	78.3 (8.09)	75.8 (8.08)
Mild Impairment (n=10)	68.9 (17.0)	59.3 (13.3)	77.7 (9.43)	71.6 (9.95)
Moderate Impairment (n=9)	91.8 (24.7)	83.4 (26.7)	85.6 (23.2)	86.1 (21.3)
Severe Impairment (n=10)	99.7 (15.5)	91.6 (16.1)	97.3 (15.4)	96.3 (14.6)

Key: hr=hour; RT_G =renal threshold
Note: eGFR ranges for each renal function group are as follows: Normal = ≥ 90 mL/min/1.73m^2; Mild = 60-89 mL/min/1.73m^2; Moderate = 30-59 mL/min/1.73m^2: Severe = 15-29 mL/min/1.73m^2

Reviewer's Comments:

- *Given the relatively small percentage of canagliflozin excreted unchanged in urine (<1%), the magnitude of the effect of renal impairment on the exposure to canagliflozin was greater than expected with 15%, 29% and 53% higher exposure in mild, moderate and severe renal impairment, respectively as compared to normal. Possible reasons could be:*
  - *Body weight in subjects with mild-severe renal impairment was 16-24% lower than in normal. Note that body weight was a statistically significant, but clinically non-relevant covariate for volume of distribution in the population PK analysis*
  - *Age mismatch with mean age in normal being lower than in renal impairment groups. Note that Age was also a statistically significant, but*

clinically non-relevant covariate for volume of distribution in the population PK analysis

- *Change in nonrenal clearance can increase exposure in renal impairment.*
- *Uremic toxins may also affect non-renal (hepatic) clearance which could increase the exposure.*

- *Mean metabolite exposures for both metabolites (M5 and M7, which are pharmacologically inactive) showed an increase with decreasing renal function. This is consistent with 32% of oral dose being renally cleared as metabolites.*
- *There was no change in plasma protein binding of canagliflozin across the different renal function groups.*
- *Hemodialysis has minimal effect on plasma concentrations and the pharmacokinetics of canagliflozin and its 2 metabolites.*
- *Consistent with the mechanism of action of canagliflozin, the mean reduction in UGE0-24 was proportional to the creatinine clearance, with UGE0-24 decreasing with increase in degree of renal impairment. The lower UGE response could be due to both less filtered glucose (due to lower GFR) and also due to less effect of canagliflozin to reduce RT_G.*
- *The sponsor has proposed no dose adjustment in mild renal impairment which is acceptable. The sponsor indicates that higher incidence of adverse events related to reduction in intravascular volume was observed in patients with moderate renal impairment and has proposed a starting dose of 100 mg for these patients. The UGE in this group is considerably reduced. Consistent with the reduced pharmacodynamic action of canagliflozin in renal impairment, the efficacy was also decreased in moderate renal impaired subjects as discussed in Section 2. Considering the marginal efficacy response as well as higher incidence of adverse events observed in this group of patients, this reviewer recommends that canagliflozin be not used in moderate renal impairment. Canagliflozin is not recommended for severe renal impaired with ESRD patients or on dialysis as efficacy is not expected.*

Hepatic Impairment: Canagliflozin PK was evaluated in an open-label, single dose study in subjects with normal hepatic function and subjects with mild or moderate hepatic impairment. Subjects were classified into 1 of 3 hepatic function groups (normal hepatic function, mild hepatic impairment, and moderate hepatic impairment) on the basis of Child-Pugh classification (N=8 per group).

Canagliflozin PK: Mean canagliflozin apparent $t_{1/2}$ values were 14.8 hours, 17.6 hours, and 13.1 hours in subjects with normal hepatic function, and in subjects with mild and moderate hepatic impairment, respectively. The mean CL/F was similar in all 3 hepatic function groups. Mean Cmax and AUCinf values for total plasma canagliflozin were similar (differed less than 11%) between the normal hepatic function and impaired (mild and moderate) groups (Table 26).

Table 26: Arithmetic Mean (SD) Total Canagliflozin Plasma Pharmacokinetic Parameters Following Administration of Canagliflozin in Subjects with Varying Degrees of Hepatic Function

(Source Study 28431754DIA1013: Pharmacokinetic Data Analysis Set)

Parameter	Normal Hepatic Function	Mild Hepatic Impairment	Moderate Hepatic Impairment
N	8	8	8
C_{max} (ng/mL)	2844 (794)	3038 (670)	2810 (1037)
t_{max} (h)[a]	1.75 [1.00-5.00]	2.00 [1.00-5.00]	2.00 [1.00-5.00]
AUC_{last} (ng.h/mL)	25072 (6845)	26910 (8624)	26704 (5811)
AUC_{∞} (ng.h/mL)	24632 (7132)[b]	27162 (8609)	26866 (5788)
$t_{1/2}$ (h)	14.8 (2.72)[b]	17.6 (4.17)	13.1 (3.05)
Vd/F (L)	270 (59.1)[b]	308 (131)	217 (61.7)
CL/F (L/h)	13.1 (3.70)[b]	12.0 (3.62)	11.6 (2.40)
Ae (%,dose)	0.479 (0.120)	0.534 (0.126)	1.47 (0.329)[c]
CL_R (L/h)	0.0632 (0.0154)	0.0674 (0.0151)	0.169 (0.0459)[c]
CL_{NR} (L/h)	13.0 (3.70)[b]	11.9 (3.61)	10.7 (2.27)[c]
CL_{CR} (mL/min)	101 (13.9)	100 (20.3)	92.2 (16.2)

[a] Median [range]

[b] n=7, as Subject 101332 was excluded from the descriptive statistics for parameters that were estimated based on the terminal phase due to unacceptable variability in the terminal phase (r^2_{adj}: 0.8322)

[c] n=6, see Section 5.2, Datasets Analyzed for description of excluded subjects

Cross-reference: attachment TablePK3, attachment TablePK5, attachment TablePK7

Canagliflozin M7 and M5 metabolites PK: Total plasma M7 concentrations increased with a decrease in hepatic function. The mean percentage of the dose recovered as M7 in urine increased with a decrease in hepatic function (22.9% and 34.5% in subjects with mild and moderate hepatic impairment, respectively, as compared to 17.2% in subjects with normal hepatic function). Geometric mean AUCinf and Cmax for subjects with mild hepatic impairment were 58% and 35% higher than normal renal function subjects, respectively. While, in moderate hepatic impairment the geometric mean AUCinf and Cmax were 113% and 58% higher than normal hepatic function subjects, respectively.

In case of M5, the total M5 AUCinf and Cmax in mild hepatic function were comparable to those in normal hepatic function subjects. While in moderate hepatic impairment, there was a 39% increase in AUCinf and 15% increase in Cmax, respectively as compared to normal hepatic function subjects.

Reviewer's comments:

- *The renal clearance of canagliflozin increased in moderate hepatic impairment (1.47% as compared to 0.48% in normal and 0.53% in mild hepatic function). This could be due to increase in unbound canagliflozin (31% increase in unbound canagliflozin AUCinf as compared to normal) in moderate hepatic impairment leading to increase in unbound drug concentration available for glomerular filtration. Considering that <1% of intact canagliflozin is excreted in the urine, the clinical relevance of this increase is most likely minimal.*
- *Plasma M7 increased with hepatic impairment, while M5 increased only in moderate hepatic impairment which could be due to changes in biliary excretion of M7 and M5. In vitro and animal data suggests that biliary excretion is one of the major routes of excretion of canagliflozin. The plasma increase with decrease in liver function suggests an altered metabolism and/or decreased biliary*

clearance of M5 and M7. As these metabolites are pharmacologically inactive, these increases are not clinically relevant.

- *No dose adjustment is needed in mild and moderate hepatic impairment.*
- *Since the effect of severe hepatic impairment on canagliflozin PK has not been evaluated, the sponsor is recommending that the drug be not used in this population. Considering there are other antidiabetic agents (e.g., saxagliptin, linagliptin) available for use in this population, the proposed recommendation seems reasonable. However, based on the observed changes in mild to moderate hepatic impairment, significant increase in canagliflozin levels that may be of a safety concern is not expected to occur in severe hepatic impairment. Therefore this reviewer is of the opinion that if canagliflozin is used in severe hepatic impairment, caution should be used.*

Effect of Age, Gender, Body weight and Race:

Based on the population PK analysis with data collected from 1526 subjects, age, BMI, gender, and race do not have a clinically meaningful effect on pharmacokinetics of canagliflozin (See Appendix, Pharmacometric Review).

Pediatric patients: Sponsor is requesting a waiver to conduct pediatric studies in children 0 to < 10 years of age. Sponsor is also requesting a deferral from providing pediatric data as required by the Pediatric Research Equity Act (PREA), for canagliflozin as a treatment for T2DM until a favorable risk/benefit ratio in adults has been established. The sponsor has submitted a pediatric plan that includes a Phase 1 study to investigate the PK/PD of canagliflozin and a Phase 3 metformin add-on study. The sponsor has requested (b) (4) The two studies proposed are:

(b) (4)

The proposed plan seems reasonable. This will be further discussed with the CDER Pediatric Research Committee (PeRC).

2.6.2 What pregnancy and lactation use information is available?

No studies were conducted in pregnant or lactating women.

Studies in lactating rats indicated that canagliflozin and its metabolites are found in milk and the radioactivity concentrations in milk were almost the same as those in plasma (See nonclinical review for details).

2.6.3 Are differences in canagliflozin exposure resulting from polymorphisms in the gene encoding UGT1A9 clinically relevant?

No.

Canagliflozin is metabolized by UGT1A9 and UGT2B7. With regard to *UGT1A9* pharmacogenetics, the applicant submitted a pharmacogenomics statistical analysis report (JNJ-28431754 – Meta-Analysis) and a population PK analysis report (JNJ-28431754 POP PK Report). The NDA included a primary analysis of *UGT1A9**3 effects on steady-state trough concentrations (n=732) and an exploratory analysis of effects on other canagliflozin PK parameters ($Cmax_{,ss}$, $AUC_{\tau,ss}$ [n=134]; M5 and M7 metabolite to parent ratios [n=66]). Phase 1, 2, and 3 clinical trials were included in the meta-analysis. The effect of UGT1A9 genotype is small and while exposures are higher on average in variant carriers, the concentrations still fall within the range of exposures observed in subjects without UGT1A9 variants (Figure 27).

In the applicant's additional exploratory analyses of other PK endpoints, dose-normalized $AUC_{\tau,ss}$ and $C_{max,ss}$ for canagliflozin were approximately 45% and 11% higher, respectively, in subjects carrying the *UGT1A9*3* allele relative to the mean concentrations in subjects without this variation. *UGTB4* genotype did not have any effect on canagliflozin C_{trough} among the 291 subjects with data available, with or without stratification by *UGT1A9* genotype.

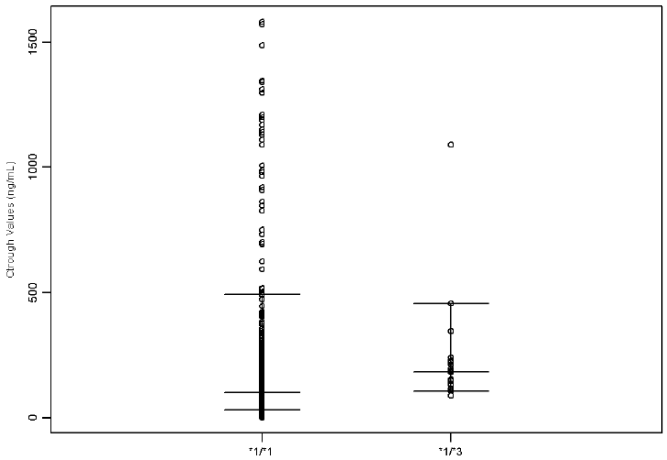


Figure 27: Effect of UGT1A9*3 polymorphism on canagliflozin trough concentration Source: Sponsor's Meta-Analysis

*UGT1A9**1/*3 genotype is associated with higher canagliflozin concentrations (C_{trough}) on average but it does not appear to be a robust or unique predictor of higher exposure.

The genotype frequency of the *UGT1A9**3 occurs in less than 5% of Caucasians and is generally not identified in other races. The effect of the increased exposure on the primary efficacy outcome is likely to be of limited clinical relevance because of the small effect size (Refer Appendix, Genomic review).

2.7 Extrinsic Factors

2.7.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.7.2 Is the drug a substrate of CYP enzymes? Is there an involvement of Phase 2 drug metabolizing enzymes?

Involvement of CYP450 enzymes in the metabolism of canagliflozin is very minimal. Based on *in vitro* studies, the metabolite M9 (a minor metabolite) appears to be formed by CYP3A4 and by CYP2D6 to a lesser extent. It was not a substrate of alcohol dehydrogenase.

The major metabolic pathway of canagliflozin in human hepatocytes is O-glucuronidation. It is metabolized to form two O-glucuronide metabolites, M5 and M7 which are formed by UGT2B4 and UGT1A9, respectively. M7 was formed in both human kidney and liver microsomes however M5 was observed only with human liver microsomes. The metabolic clearance by liver was 9-fold higher than the kidney. There was no metabolism of canagliflozin in human intestinal microsomes *in vitro*, indicating that the role of intestinal UGTs is negligible. As per guidance, the sponsor has conducted a DDI study with a general inhibitor of UGTs, probenecid as well as compared the PK of canagliflozin between different genotypes of UGT1A9. The sponsor has also conducted a study to see the effect of a non-specific inducer of UGTs, rifampin on canagliflozin PK.

2.7.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Canagliflozin appears to have inhibitory activity for some of the CYP enzymes. It was found to be a moderate inhibitor of CYP2B6 (IC_{50} = 16 μM). It inhibited CYP3A4 when testosterone was the substrate (IC_{50} = 27-47 μM) while it had no effect on midazolam metabolism (IC_{50} > 100 μM). The IC_{50} values for canagliflozin against CYP isoforms 1A2 and 2A6 were > 100 μM (highest test concentration in the assay). The IC_{50} values for the inhibition of CYP isoforms and the R value (Ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and in the presence of the interacting drug) calculated as per DDI draft guidance is shown in Table 27 below.

Table 27: Evaluation of DDI potential for canagliflozin

CYP Enzymes	[I], μM	IC_{50}, μM	Ki, μM	R = 1 + [I]/ Ki
CYP3A4	10.5	27	13.5	**1.78**
CYP2C9	10.5	55	27.5	**1.40**
CYP2C19	10.5	39	19.5	**1.54**
CYP2B6	10.5	16	8	**2.31**
CYP2D6	10.5	65	32.5	**1.32**
CYP2C8	10.5	75	37.5	**1.28**
CYP2E1	10.5	18	9	**2.11**

[I] represents the mean steady-state total Cmax following the highest proposed dose (300 mg = 10.5 μM or 4678 ng/mL).
Ki = IC_{50}/2 assuming competitive inhibition.
R = Ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and in the presence of the interacting drug

The cut-off value for R for all these CYPs was > 1.1 (the value for a drug to be assumed as a likely CYP inhibitor *in vivo)*. Therefore, the potential for canagliflozin to inhibit all these CYPs *in vivo* cannot be ruled out. Hence sponsor has conducted several DDI studies with substrates of these enzymes (e.g., simvastatin, glyburide, oral contraceptive, and warfarin).

Both M5 and M7 (*O*-glucuronide conjugates of canagliflozin) did not show CYP inhibition at clinically relevant concentrations for all CYP isoforms tested in the study. The IC_{50} values for M5 and M7 against almost all CYP isoforms were > 100 μM (highest test concentration in the assay) with the exception of CYP2B6 and 2C8 for M7. M7 showed a weak inhibition against CYP2B6 (bupropion hydroxylation) and CYP2C8 (N-desthylamodiaquine) with IC50 values of 55 μM and 64 μM, respectively.

Canagliflozin at concentrations up to 15 μM did not induce CYPs 1A2, 2B6 and 3A4. Also no induction occurred for 2C9 and 2C19 (highest concentration tested for these was 10 μM) *in vitro* in cryopreserved hepatocytes. Similarly, the metabolites M5 and M7 were not found to be inducers of CYP1A2, 2B6 or 3A4 in human hepatocytes.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes? Are there other metabolic/transporter pathways that may be important?

The sponsor evaluated the interaction of canagliflozin with various transporters: P-glycoprotein, Multidrug Resistance Associated Protein-2 (MRP2), Organic Anion Transporting Polypeptide 1B1 (OATP1B1), Organic Anion Transporter 1 & 3 (OAT1 & 3), Organic Cation Transporter 1 & 2 (OCT 1 & 2), and Sodium taurocholate cotransporting polypeptide (NTCP).

P-glycoprotein: Based on Caco-2 data, the transport of 14C-JNJ28431754 across the monolayers was affected by apically located efflux pump and this efflux was inhibited upto 95% by verapamil, a P-glycoprotein inhibitor. Canagliflozin did not have much inhibitory effect on paclitaxel, a P-glycoprotein substrate. These observations were further evaluated in MDR1 transfected MDCKII cell lines. The efflux ratio was 12 indicating that canagliflozin is a substrate of MDR1 (P-glycoprotein). Sponsor conducted a DDI study with cyclosporin (P-glycoprotein inhibitor) to see the impact on canagliflozin PK.

Canagliflozin also inhibited P-glycoprotein mediated digoxin transport by 1-4 fold as compared to 33-fold in presence of positive control cyclosporine in these cells. The IC_{50} was determined to be 19.3 μM. The ratio of $[I]/IC_{50}$, where [I] represents the mean steady-state total Cmax following the highest proposed dose (300 mg = 10.5 μM or 4678 ng/mL) was found to be 0.54. As this ratio is > 0.1 an *in vivo* DDI study with a P-glycoprotein substrate (digoxin) was conducted by the sponsor as per the DDI draft guidance recommendations.

The evaluation of M5 and M7 as substrates or inhibitors of P-glycoprotein was done in MDR1 transfected LLC-PK1 cell lines. Both metabolites were not determined to be substrates or inhibitors of MDR1 *in vitro*.

MRP2: Studies in MRP2 transfected cell line, showed an efflux ratio of 7 for canagliflozin, indicating that it is a substrate of MRP2. Canagliflozin also inhibited MRP2 mediated etoposide transport by 1.2 -9 fold as compared to 7-fold by positive control cisplatin in these cells. The IC_{50} was determined to be 21.5 μM. The ratio of $[I]/IC_{50}$ was found to be 0.49. Currently no recommendations exist for conducting an *in vivo* study with a MRP2 substrate or inhibitor and the potential for canagliflozin to inhibit MRP2 or the effect of MRP2 inhibition on canagliflozin PK was not further evaluated *in vivo*.

The evaluation of M5 and M7 as substrates or inhibitors of MRP2 was not done.

Uptake transporters- NTCP, OAT1, OAT3, OATP1B1, OCT1and OCT2: Xenopus laevis (frog) oocytes injected with human hNTCP, hOAT1, hOAT3, hOATP1B1 (hOATP2), hOCT1, and hOCT2 transporter cRNA were used as test system and water injected oocytes served as background control. The uptake was negative for all indicating that canagliflozin is not a substrate for these transporters. Canagliflozin did not inhibit OAT1, OAT3, OCT1 and OCT2. There was a slight inhibition (< 30%) of NTCP, while conclusions regarding inhibition of OATP1B1 could not be made.

Similarly, M5 and M7 were not substrates of NTCP, OAT1, OATP1B1, OCT1, or OCT2. While M5 did not inhibit any of these transporters, M7 showed inhibition towards NTCP (86%), OAT3 (54%) and OATP1B1 (65%). The inhibition was conducted at one concentration (100 μM) and IC50 was not calculated.

2.7.5 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Canagliflozin was not an inhibitor of uric acid transporter (URAT1) *in vitro*.
The SGLT2 inhibition by canagliflozin reduces sodium and glucose reabsorption in the proximal convoluted tubule. On the other hand thiazide diuretics inhibit sodium reabsorption in the distal convoluted tubule. Due to canagliflozin's effect, more sodium can be presented in the distal convoluted tubule and can affect the PD of thiazide diuretics. Therefore, sponsor conducted a DDI study with hydrochlorthiazide. Coadministration of canagliflozin with hydrochlorthiazide did not alter the PK and PD of either drug (Table 28).

DDI with warfarin showed no changes in the PK of S- and R-warfarin. Consistent with no PK changes of warfarin, there was no effect of canagliflozin on the PD of warfarin. The mean INRmax values attained with a single 30 mg warfarin dose was 2.07 with a range of 1.40 to 2.70. Similar INR results were seen when warfarin was administered with 300 mg canagliflozin.

2.7.6 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes.

Canagliflozin has the potential to inhibit CYP enzymes *in vivo* (Table 27). It also may cause inhibition of transporters such as P-glycoprotein and MRP2 *in vivo*. Further, canagliflozin is metabolized by UGT enzymes (1A7 and 2B4) which can be inhibited or induced and has the potential to change canagliflozin systemic exposure.

2.7.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Several DDI studies were conducted by the sponsor as shown below. Table 28 summarizes the effect of co-administered drugs on PK of canagliflozin and Table 29 summarizes the impact of canagliflozin on the PK of co-administered drugs.

Table 28: Effect of Co-Administered Drugs on Systemic Exposures of Canagliflozin

Co-Administered Drug (Dose, Regimen[1])	Major Interaction Pathway	Canagliflozin Dose and Regimen[1]	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect=1.0	
			AUC[2] (90% CI)	C_{max} (90% CI)
Cyclosporine (400 mg)	p-Glycoprotein and MRP2 Transporter inhibition by cyclosporine	300 mg QD for 8 days	**1.23 (1.19; 1.27)**	1.01 (0.91; 1.11)
Ethinyl estradiol and levonorgestrel (0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel)	Concomitant drug	200 mg QD for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)
Hydrochlorothiazide (25 mg QD for 35 days)	Diuretic (PD interaction)	300 mg QD for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
Metformin (2,000 mg)	Renal excretion by hOCT-1 and h-OCT-2	300 mg QD for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)
Probenecid (500 mg BID for 3 days)	Probenecid is a UGT inhibitor and certain transporters (MRP2, OATP, OAT1, and OAT3)	300 mg QD for 17 days	1.21 (1.16; 1.25)	**1.13 (1.00; 1.28)**
Rifampin (600 mg QD for 8 days)	UGT inducer	300 mg	**0.49 (0.44; 0.54)**	**0.72 (0.61; 0.84)**

[1] Single dose unless otherwise noted
[2] AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
QD = once daily; BID = twice daily
Bolded values indicate that the geometric mean ratio or 90 % CI is outside 80%-125% limit

Reviewer Comments:

- *Co-administration with cyclosporine increased the AUC of canagliflozin by 23% with no change in Cmax. Sponsor did not analyze metabolites concentrations in this study. This increase is likely due to inhibition of P-glycoprotein or other transporters by cyclosporine. This increase in 23% does not necessitate any dose-adjustments.*
- *There was no effect of oral contraceptives, metformin and hydrochlorothiazide on canagliflozin PK.*
- *There was no change in the urinary glucose excretion of canagliflozin in presence of hydrochlorothiazide. The renal threshold of glucose was greater when the two drugs were co-administered (by ~5 mg/dL). Considering that canagliflozin itself can cause this threshold to decrease from baseline by 120 – 140 mg/dL, this change of 5 mg/dL is not going to be clinically meaningful.*

- *Probenecid due to its UGT inhibition effect, increased the plasma canagliflozin Cmax and AUCtau by 13% and 21%, respectively. While, M7 Cmax and AUCtau increased by 29% and 30%, respectively in presence of probenecid. (42% less M7recovered in urine). Similarly, M5 exposures were also increased, 29% and 46%, Cmax and AUC, respectively in presence of probenecid. (72% less M5 in urine). The effect of probenecid on metabolites M5 and M7 cannot be explained solely by probenecid-induced UGT inhibition, as the mean metabolite-to-parent ratios for AUCτ,ss and Cmax,ss for both M5 and M7 increased with probenecid treatment, suggesting that inhibition of renal and biliary transport of these metabolites by probenecid may contribute to these findings. These changes are not clinically relevant.*
- *Rifampin is a UGT inducer and as a result of this induction, mean plasma Cmax and AUCinf values for canagliflozin were approximately 30% and 52% lower, respectively, and mean apparent t1/2 was approximately 13% shorter, following the co-administration with rifampin as compared to when canagliflozin was administered alone. Mean plasma Cmax and AUCinf values for M7 were approximately 23% higher and 36% lower, respectively, and mean apparent t1/2 was approximately 20% shorter, following the co-administration of canagliflozin with rifampin as compared to when canagliflozin was administered alone. Mean plasma Cmax values for M5 were approximately 49% higher, and mean AUCinf and apparent t1/2 was similar, following co-administration of canagliflozin with rifampin as compared to when canagliflozin was administered alone. The metabolites exposure in plasma did not increase as expected. This suggests that the biliary excretion may also have been induced due to induction of biliary transporters. Also consistent with this speculation is that the excretion of M7 and M5 in urine were decreased in presence of rifampin. This reviewer recommends that patients be on 300 mg canagliflozin dose when rifampin is co-administered since there may be a greater potential of loss of efficacy at 100 mg dose and HbA1c should be monitored.*

Table 29: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug (Dose, Regimen[1])	Major Interaction Pathway	Canagliflozin Dose and Regimen[1]	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0		
				AUC[2] (90% CI)	C_{max} (90% CI)
Acetaminophen (1000 mg)	Effect on GI motility by canagliflozin	300 mg BID for 25 days	acetaminophen	1.06[3] (0.98; 1.14)	1.00 (0.92; 1.09)
Digoxin (0.5 mg QD first day followed by 0.25 mg QD for 6 days)	P-glycoprotein substrate and inhibition by canagliflozin	300 mg QD for 7 days	digoxin	**1.20 (1.12; 1.28)**	**1.36 (1.21; 1.53)**
Ethinyl estradiol and levonorgestrel (0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel)	CYP3A4 inhibition by canagliflozin	200 mg QD for 6 days	ethinyl estradiol	1.07 (0.99; 1.15)	**1.22 (1.10; 1.35)**
			levonorgestrel	1.06 (1.00; 1.13)	**1.22 (1.11; 1.35)**
Glyburide (1.25 mg)	CYP2C9 inhibition by canagliflozin	200 mg QD for 6 days	glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)
Hydrochloro-thiazide (25 mg QD for 35 days)	Diuretic (PD interaction)	300 mg QD for 7 days	hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin (2000 mg)	Concomitant drug	300 mg QD for 8 days	metformin	**1.20 (1.08; 1.34)**	1.06 (0.93; 1.20)
Simvastatin (40 mg)	CYP3A4 inhibition by canagliflozin	300 mg QD for 7 days	simvastatin	**1.12 (0.94; 1.33)**	**1.09 (0.91; 1.31)**
			simvastatin acid	**1.18 (1.03; 1.35)**	**1.26 (1.10; 1.45)**
Warfarin (30 mg)	CYP2C9 inhibition by canagliflozin	300 mg QD for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (0.98; 1.03)	1.05 (0.99; 1.12)

[1] Single dose unless otherwise noted

[2] AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses

[3] AUC_{0-12h}

QD = once daily; BID = twice daily; INR = International Normalized Ratio

Bolded values indicate that the geometric mean ratio or 90 % CI is outside 80%-125% limit

Reviewer Comments:

- *There was no effect of canagliflozin on acetaminophen, glyburide, hydrochlorothiazide and warfarin PK.*
- *Canagliflozin at steady-state increased the metformin plasma AUC by 20% without changes in its Cmax. These changes were not due to renal interaction as there were no changes in metformin renal excretion in presence of canagliflozin. This change does not translate to the need of dose adjustment for metformin when co-administered with canagliflozin.*
- *Digoxin trough plasma concentrations were comparable on Days 5, 6 and 7 of both treatments suggesting steady-state achievement by Day 5. Mean trough levels were 18% higher in presence of canagliflozin. The AUC0-24 and Cmax values of digoxin were approximately 20% and 36% higher, respectively, when digoxin was co-administered with canagliflozin compared to when digoxin was administered alone. The mean percentage of the digoxin dose excreted in urine and CLR were similar for both treatments. There was no effect on Tmax of digoxin. No subjects exceeded the upper limit of the therapeutic range of digoxin (2.0 ng/mL) beyond the 6-hour timepoint. The current recommendation to monitor digoxin levels when it is co-administered with canagliflozin is acceptable.*
- *The Cmax of both oral contraceptive components was increased (~20%) in presence of canagliflozin. The dose of canagliflozin used in this study was 200 mg, while 300 mg is the highest proposed dose. Based on another DDI study with a sensitive CYP3A substrate, simvastatin the exposure of the OC components is not expected to increase significantly as compared to those seen following 200 mg canaglifozin. No notable protocol deviations occurred during this trial. There were no major AEs. Overall no dose adjustment is needed.*
- *The increase in Cmax for simvastatin and simvastatin acid was 9% and 18%, respectively, while the increase in AUC was 12% and 26%, respectively. Although the drug levels increased, plasma HMG-CoA reductase activity was not changed (as assessed in an ex-vivo assay which measured the inhibition of HMG-CoA reductase by simvastatin using a radioactive substrate). The sponsor conducted this study with the highest proposed dose of canagliflozin (300 mg) and 40 mg of simvastatin. Although, the sponsor didn't use the lowest dose of the substrate to maximize the sensitivity, the potential of increased interaction with canagliflozin is not likely. No dose adjustment for simvastatin is recommended.*

2.7.8 Are there any other questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Potential for inhibition of CYP2B6*:* Sponsor has conducted DDI studies with CYP3A4 and 2C9 substrates. As mentioned above, there was no effect of canagliflozin on the PK of substrates of CYP3A4 and 2C9; therefore, the interaction with other CYPs with similar or lower R value (e.g., for CYP2C8) is also of no concern. PBPK modeling confirmed the lack of DDI *in vivo* using simvastatin, ethinyl estradiol, and S-warfarin as substrates. Sponsor has not conducted any DDI studies with substrates of CYP2B6 and CYP2E1 whose R values were over the 1.1 cut-off values and higher than those for CYP3A4 and

2C9. Sponsor has used PBPK modeling to address the DDI potential with CYP2B6 substrates. PBPK modeling using bupropion (a CYP2B6 substrate) did not show significant increase of the AUC (less than 1.25). This reviewer agrees with the sponsor's PBPK modeling effort and agrees that this work is sufficient to support the conclusion that *in vivo* inhibition of CYP2B6 by canagliflozin is not likely. CYP2E1 inhibition by canagliflozin is not of a concern as this enzyme is not a major player in metabolism of drugs in general.

Potential of chiral conversion in vivo: The chemical structure of (b) (4) is very similar to that of (b) (4) (see structures below). Anomerization between (b) (4) requires a (b) (4) this conversion is considered unlikely to occur *in vivo* but was evaluated in a subset of subjects from study DIA1023.

Samples from 10 subjects (2 subjects on placebo; 2 subjects on 50 mg dose; 1 subject on 100 mg dose and 5 subjects receiving 300 mg canagliflozin dose) were assayed from the predose (5 subjects), 3-, 8-, and 12-hour time points after dosing on Day 1 and from the 3-, 8-, and 12-hour time points on Day 7 using a LC-MS/MS method developed for this screening purpose. Of the samples that were assayed, only 3 samples from 2 subjects had concentrations of the (b) (4) slightly higher than the limit of quantitation of 5 ng/mL. The concentrations were 6.83 ng/mL, 5.15 ng/mL and 5.05 ng/mL on Day 7 at 3 h for one subject and at 3h and 12 h time-point for another subject, respectively. Concentrations at all other time-points on both Day1 and Day 7 were below the 5 ng/mL limit of quantitation.

In the same study, the Cmax of canagliflozin following the 100 mg and 300 mg was 1227 ng/mL and 4678 ng/mL on Day 7, respectively. Therefore, the canagliflozin plasma concentrations are approximately 180-250 times higher at the 100 mg dose and 700-900

times higher at the 300 mg canagliflozin dose than that of the [(b) (4)] r and suggests that the [(b) (4)] is not clinically significant *in vivo*.

2.8 General Biopharmaceutics

2.8.1 What is relative bioavailability between the formulations used in early phase 1 trials to the tablet formulation used in phase 2 and 3 trials?

Canagliflozin formulations used in early Phase 1 and Phase 2 trials were developed using [(b) (4)], while the formulations used in Phase 3 trials were developed using [(b) (4)] (Table 30). [(b) (4)]

Table 30: Core tablet quantitative ingredient statement per Unit dose

Component	Quality Reference	[(b) (4)]	
		% w/w	% w/w
Canagliflozin	Company Standard	[(b) (4)]	
[(b) (4)]	NF		
Microcrystalline Cellulose	NF		
Lactose Anhydrous	NF		
Croscarmellose Sodium	Ph. Eur./NF		
Hydroxypropyl Cellulose	Ph. Eur./NF		
Magnesium Stearate	Ph. Eur./NF		
[(b) (4)]	USP		
	Total	100.00	100.00

[(b) (4)]

Table generated by the Sponsor

A Phase 1 bioequivalence study (Study DIA1017) was conducted to assess the relative bioavailability of [(b) (4)] tablets (test) with respect to [(b) (4)] tablets (reference) under fasted conditions in healthy subjects. Results indicated that the two formulations were bioequivalent (Figure 28).

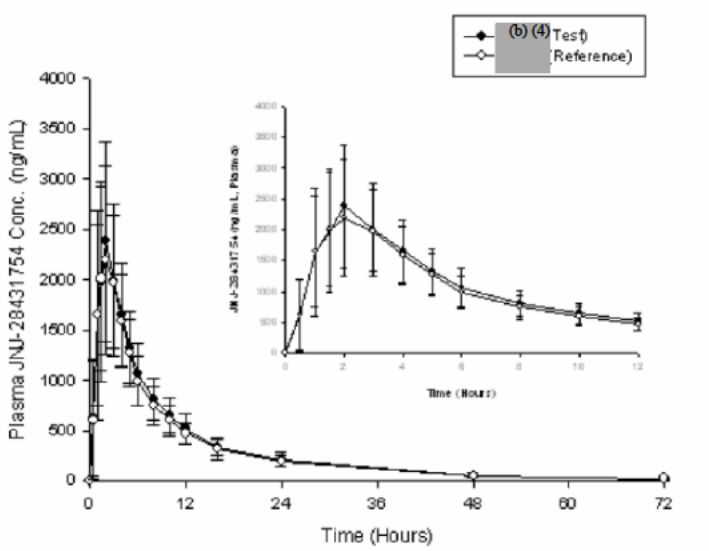
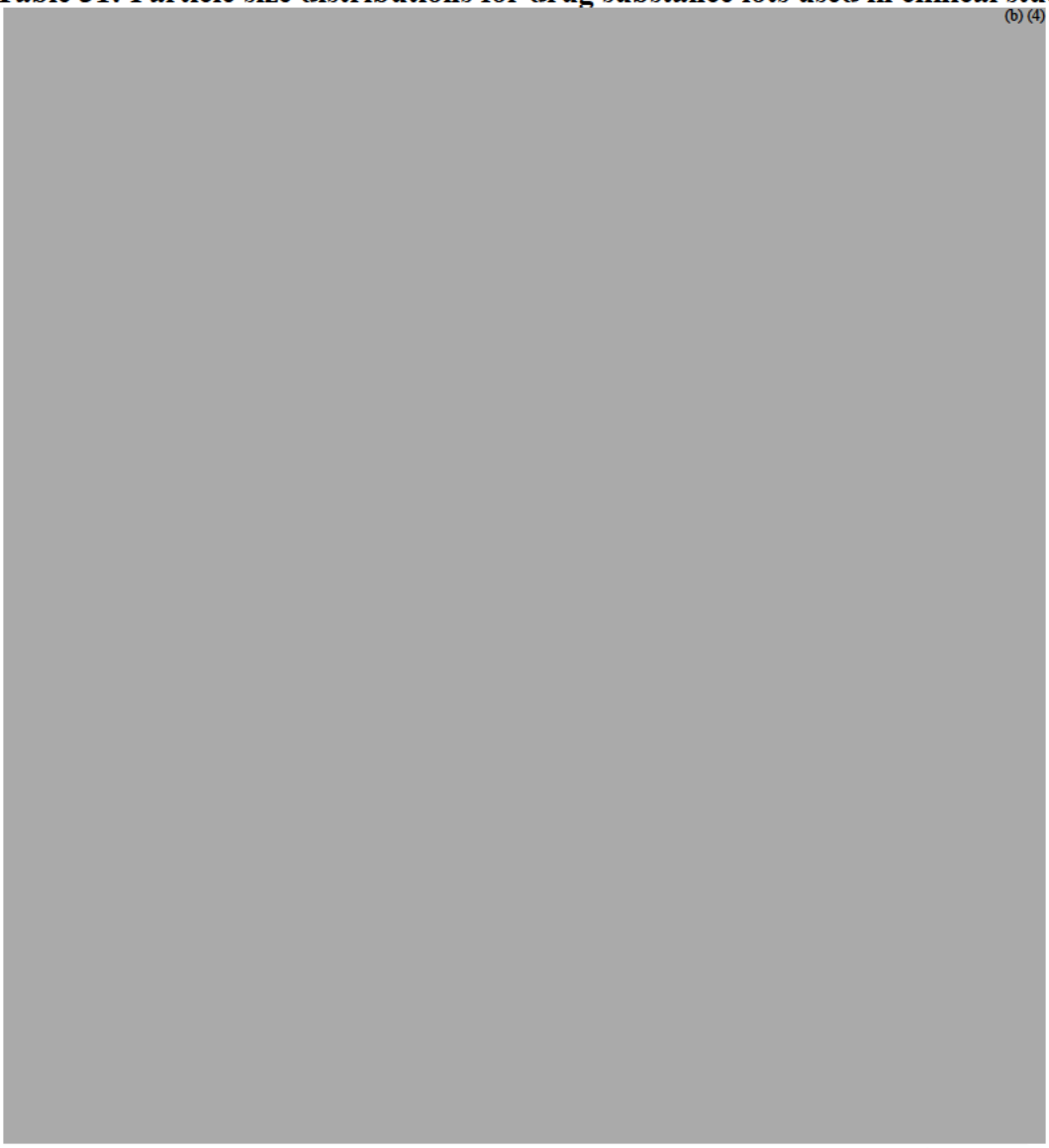


Figure 28: Mean (SD) plasma concentration-time profile of canagliflozin following a single oral administration of a 30 mg (b) (4) tablet and a single oral administration of a 300 mg (b) (4) tablet in healthy subjects.
Source: Sponsor's study report for DIA1017

During the API development of canagliflozin, (b) (4)

Table 31: Particle size distributions for drug substance lots used in clinical studies



An examination of the table shows that only two early batches of the (b) (4) API had a broader particle size distribution (Lots ZR600348PFA021 and ZR600348PFA031) and that for all the other (b) (4) lots, the particle size distribution is fairly similar to those of the (b) (4) lots. The (b) (4) lots ZR600348PFA021 and ZR600348PFA031 were used only in six Phase 1 and two Phase 2 studies, not in any of the Phase 3 studies. The (b) (4) lots used in Phase 3 studies have particle size distributions that are fairly similar to those of the (b) (4) lots. Overall, the bulk of the clinical studies used API particle size distributions that are fairly similar, regardless of whether they are (b) (4)

2.8.2 *How is the proposed to-be-marketed formulation linked to the clinical trial formulation?*

The to-be-marketed formulation will be developed using [redacted] (b) (4) and is compositionally the same as the Phase 3 clinical trial formulation.

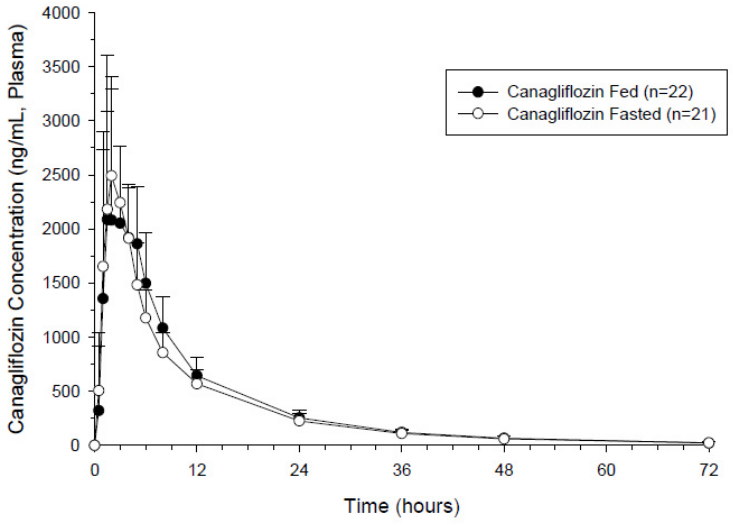
2.8.3 *What is the effect of food on the bioavailability of the tablets?*

Study DIA1043 evaluated the effect of co-administration of a standardized high-fat breakfast on the oral bioavailability of 300 mg canagliflozin. Results show that peak plasma concentrations (C_{max}) of canagliflozin were 3026 ng/mL and 2975 ng/mL following administration with and without food, respectively (Figure 29).

Time to peak (T_{max}) values was similar for both treatments with a median value of 2.0 hours (range from 1.0 to 4.0 hours when administered without food; range from 1.0 to 5.0 hours when co-administered with food). Mean apparent elimination half-life ($t_{1/2}$) of canagliflozin was 12.9 hours in subjects under fasting conditions and 12.6 hours in subjects under fed conditions.

Absence of food effect on canagliflozin bioavailability was established as the 90% CIs for the ratios of the geometric means between fed and fasted treatments were contained within the pre-specified equivalence limits of 80.00% to 125.00% for C_{max} and AUCs.

Canagliflozin tablets may be administered to subjects without regard to meals.



Source: Study report DIA1043

Figure 29: Canagliflozin plasma concentration-time profile in presence of food and under fasted condition

2.8.4 What is absolute oral bioavailability of canagliflozin following oral administration?

Study DIA1021 evaluated the absolute oral bioavailability of canagliflozin following single-dose administration of 300 mg canagliflozin and a simultaneous intravenous dose of 10 µg ^{14}C-canagliflozin in healthy subjects. Extent of biliary excretion of canagliflozin was also evaluated in this study. Canagliflozin used in this study for oral administration were manufactured by the (b) (4).

Results from this study show that the mean absolute oral bioavailability of canagliflozin was 64.9%. Unchanged [^{14}C]-canagliflozin was the major circulating component in plasma. Following oral administration of 300 mg canagliflozin, peak concentrations of 2504 ng/mL were achieved at a median T_{max} of 1.5 hours. Mean apparent elimination half-life of canagliflozin was 11.6 hours. Following a 15 minute intravenous infusion of a 10 µg micro-dose of [^{14}C]-canagliflozin (200 nCi), apparent terminal elimination half-lives of 6.88 and 9.51 hours were noted for unchanged [^{14}C]-canagliflozin and total [^{14}C] radioactivity, respectively.

Approximately 34.1% of the administered radioactive intravenous dose was recovered in feces, indicating biliary excretion as one of the major elimination pathways for total [^{14}C] radioactivity. Enterohepatic circulation of canagliflozin appeared to be negligible. Mean cumulative urinary excretion of the total [^{14}C] radioactivity over 70.25 hours was 34.5%.

2.9 Analytical

2.9.1 How are the active moieties identified and measured in the plasma/serum?

Canagliflozin was evaluated in human plasma and urine using validated LC/MS/MS methods. The two O-glucuronide metabolites (M5 and M7) of canagliflozin were evaluated in human plasma using a validated LC/MS/MS method.

Plasma samples of canagliflozin collected in (b) (4)

Canagliflozin was detected by LC-MS/MS using a (b) (4) spectrometer using a (b) (4).

The following parameters were used in the assay:

Compound	Q1 Mass (m/z)	Q3 Mass (m/z)	Dwell Time (msec)
Canagliflozin	(b) (4)	(b) (4)	(b) (4)
(b) (4))	(b) (4)	(b) (4)	(b) (4)

2.9.2 What bioanalytical methods are used to assess concentrations?

LC/MS/MS was used to measure the concentrations of canagliflozin and its metabolites M5, and M7 in plasma and urine.

Listed in Table 32 is a summary of analytical methods.

Table 32: Summary of Bioanalytical methods for Canagliflozin, M5 and M7 from Clinical Studies

No	Study No	Study Title	Analytes	Validation Range	Assay Performance description
1	BA1095	Validation (full) of an LC-MS/MS method for the determination of JNJ-28431754 in human EDTA plasma.	Canagliflozin (JNJ-28431754)	5.00 – 10000 ng/mL	Intra-assay Precision (%CV): ≤6.3% Inter-assay Precision (%CV): ≤3.5% Intra-assay Accuracy (% Diff): ≤6.8% Inter-assay Accuracy (%Diff): ≤3.1% Freeze/Thaw Stability: 3 cycles Bench Top Stability: 24 hrs Long-term Stability: 1084 days
2	BA1101	Validation of an LC-MS/MS Method for the Determination of JNJ- 28431754 in Human EDTA Plasma	Canagliflozin (JNJ-28431754)	5.0 – 10000 ng/mL (50.0 – 100000 ng/mL for diluted samples)	Intra-assay Precision (%CV): ≤3.4% Inter-assay Precision (%CV): ≤3.8% Intra-assay Accuracy (% Diff): ≤-1.8% Inter-assay Accuracy (%Diff): ≤-2.6%

No	Study No	Study Title	Analytes	Validation Range	Assay Performance description
					Freeze/Thaw Stability: 4 cycles at -20°C Bench Top Stability: 72 hrs at RT for spiked human EDTA plasma, 24 hrs at RT for spiked human EDTA blood Long-term Stability: 194 days for spiked EDTA plasma Extract Stability: 4 days in autosampler at RT
3	BA10084	Validation (full) of an LC-MS/MS method for the determination of JNJ-28431754 in human K2EDTA plasma.	Canagliflozin (JNJ-28431754)	5.0 – 10000 ng/mL (50.0 – 100000 ng/mL for diluted samples)	Intra-assay Precision (%CV): ≤6.9% Inter-assay Precision (%CV): ≤5.9% Intra-assay Accuracy (% Diff): ≤11.8% Inter-assay Accuracy (%Diff): ≤10.6% Freeze/Thaw Stability: 6 cycles Bench Top Stability: 4 hrs on melting ice or 4 hrs at RT for spiked EDTA blood, 72 hrs at RT for spiked EDTA plasma Long-term Stability: 161 days in spiked plasma Extract Stability: 167 hrs at RT (15°C – 30°C) or refrigerated (2°C – 8°C)
4	BA1273	Validation (partial) of a high throughput LC-MS/MS method for the determination of JNJ-28431754 in human EDTA plasma.	Canagliflozin (JNJ-28431754)	5.0 – 10000 ng/mL (50.0 – 100000 ng/mL for diluted samples)	Intra-assay Precision (%CV): ≤8.3% Intra-assay Accuracy (% Diff): ≤3.0% Freeze/Thaw Stability: 6 cycles for K_2EDTA plasma Bench Top Stability: 24 hrs at RT, 2 hrs at 37°C for spiked K_3EDTA blood, 4 hrs at RT and 4

No	Study No	Study Title	Analytes	Validation Range	Assay Performance description
					hrs on melting ice for K_2EDTA blood; 72 hrs at RT for spiked K_3EDTA and K_2EDTA plasma Long-term Stability: 1084 days in spiked K_3EDTA plasma, 161 days in spiked K_2EDTA plasma Extract Stability: 168 hrs at RT (15°C – 30°C) or refrigerated (2°C – 8°C)
5	BA1345	Validation (full) of a LC-MS/MS method for the determination of JNJ-28431754 in human EDTA plasma.	Canagliflozin (JNJ-28431754)	5.00 – 5,000 ng/mL 25.0 – 20,000 ng/mL (for up to 5-fold diluted samples)	Intra-assay Precision (%CV): ≤3.6% Inter-assay Precision (%CV): ≤4.3% Intra-assay Accuracy (% Diff): ≤3.1% Freeze/Thaw Stability: 5 cycles Bench Top Stability: 2 hrs on melting ice and at RT for spiked human EDTA blood, 73 hrs at RT for spiked human EDTA plasma Long-term Stability: 8 days in spiked plasma at -20°C (light) and -70°C (dark) Extract Stability: 143 hrs at 10°C in dark.
6	BA1763	Validation (full) of an LC/MS/MS method for the determination of JNJ-41980874 and JNJ-41488525 in human EDTA plasma	M5 (JNJ-41980874) M7 (JNJ-41488525)	5.00 - 10000 ng/mL 50 - 100000 ng/mL (for up to 10-fold diluted samples)	Intra-assay Precision (%CV): ≤7.8% Inter-assay Precision (%CV): 8.9% Intra-assay Accuracy (% Diff): ≤15.2% Inter-assay Accuracy (%Diff): 9.0% Freeze/Thaw Stability: 6 cycles Bench Top Stability: 2 hrs on melting ice, at RT,

No	Study No	Study Title	Analytes	Validation Range	Assay Performance description
					and at 37°C for spiked human EDTA blood, 72 hrs at RT for spiked human EDTA plasma Long-term Stability: 424 days in spiked plasma Extract Stability: 97 hrs
7	08J0002	Analytical method validation for the determination of unchanged TA-7284 concentrations in human plasma by LC-MS-MS	Canagliflozin (JNJ-28431754)	1 – 2000 ng/mL	Intra-assay Precision (%CV): ≤3.5% Inter-assay Precision (%CV): ≤7.1% Intra-assay Accuracy (% Diff): ≤7.3% Inter-assay Accuracy (%Diff): ≤3.6% Extract Stability: up to 87 hrs in autosampler at 10°C
8	08J0003	Analytical method validation for the determination of unchanged TA-7284 concentrations in human urine by LC-MS-MS	Canagliflozin (JNJ-28431754)	1 – 2000 ng/mL	Intra-assay Precision (%CV): 2.5% Inter-assay Precision (%CV): ≤3.2% Intra-assay Accuracy (% Diff): ≤12.5% Inter-assay Accuracy (%Diff): ≤15.0% Extract Stability: up to 72 hrs in autosampler at 10°C
9	JCL071431	Analytical Method Validation for the Determination of TA-7284 in Human Urine by High-Performance Liquid Chromatography/Tandem Mass Spectrometry	Canagliflozin (JNJ-28431754)	1.02 – 2040 ng/mL	Intra-assay Precision (%CV): ≤7.5% Inter-assay Precision (%CV): ≤7.6% Intra-assay Accuracy (% Diff): ≤8.2% Inter-assay Accuracy (%Diff): ≤8.2% Freeze/Thaw Stability: 3 cycles Bench Top Stability: 6 hrs at RT and 48 hrs at 5°C Long-term Stability: 98 days at -20°C

No	Study No	Study Title	Analytes	Validation Range	Assay Performance description
					Extract Stability: up to 77 h in autosampler at 10°C
10	JCL071421	Analytical Method Validation for the Determination of TA-7284 in Human Plasma by High-Performance Liquid Chromatography/Tandem Mass Spectrometry	Canagliflozin (JNJ-28431754)	1.02 – 2040 ng/mL	Intra-assay Precision (%CV): ≤3.8% Inter-assay Precision (%CV): ≤5.1% Intra-assay Accuracy (% Diff): ≤2.8% Inter-assay Accuracy (%Diff): ≤9.1% Freeze/Thaw Stability: 3 cycles Bench Top Stability: 6 hrs at RT and at 5°C Long-term Stability: 98 days at -20°C Extract Stability: up to 76 h in autosampler at 10°C

3 Detailed labeling recommendation

Labeling comments will be addressed in a separate review.

4 Appendix

4.1 Pharmacogenomics Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA Number	NDA 204042
Submission Date	05/31/2012
Applicant Name	Janssen Research and Development
Generic Name	Canagliflozin
Proposed Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Primary Reviewer	Lyle Canida, Pharm.D., M.S.
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

1 Background

Canagliflozin is a member of a new class of drugs known as sodium glucose co-transporter 2 (SGLT2) inhibitors. Glucose is freely filtered through the renal glomerulus and then reabsorbed in the proximal tubules, mostly via SGLT2 transporters. Inhibition of SGLT2 has been shown to decrease renal glucose reabsorption, increase urinary glucose excretion (UGE), and lower plasma glucose. Additional effects of UGE are diuresis, which has the potential for reductions in systolic blood pressure, and caloric loss, which had the potential for reduction in body weight.

Canagliflozin is metabolized by O-glucoronidation, mainly by *UGT1A9* and *UGT2B4*, to two inactive metabolites. CYP3A4-mediated metabolism of canagliflozin is minimal (approximately 7%) in humans. *UGT1A9* has a polymorphism, M33T (also referred to as *3), that results in substrate-specific changes in metabolic activity. The sponsor evaluated the effect of this variant on canagliflozin concentrations in several clinical trials. The purpose of this review is to evaluate the clinical relevance of the effect of *UGT1A9* polymorphisms on canagliflozin pharmacokinetics.

2 Submission Contents Related to Genomics

With regard to *UGT1A9* pharmacogenetics, the applicant submitted a pharmacogenomics statistical analysis report (JNJ-28431754 – Meta-Analysis) and a population PK analysis report (JNJ-28431754 POP PK Report). JNJ-28431754 included a primary analysis of *UGT1A9**3 effects on steady-state trough concentrations (n=732) and an exploratory analysis of effects on other canagliflozin PK parameters ($Cmax_{,ss}$, $AUC_{\tau,,ss}$ [n=134]; M5 and M7 metabolite to parent ratios [n=66]).

Phase 1, 2, and 3 clinical trials were included in the meta-analysis as listed below in table 1. Participation in PGx analysis was optional in some of the studies and DNA samples were not available for approximately half of the subjects across the trials.

Table 1. Clinical Trials used in PGx Meta-analysis

Study	Description	N	Canagliflozin dose	PK Endpoints
Phase 1				
DIA1007	Multiple dose PK/PD and safety study in patients with T2DM insulin dependent	29	100mg QD 300mg BID	$Cmax_{,ss}$, $AUC_{\tau,ss}$, C_{trough} of canagliflozin on Day 27
DIA1023	Single and Multiple dose PK/PD Study in Patients with T2DM	36	PBO 50mg QD 100mg QD 300mg QD	$Cmax_{,ss}$, $AUC_{\tau,ss}$ of canagliflozin, M5, and M7 on Days 1 and 7
DIA1028	DDI with Metformin in healthy subjects	14	300mg QD	$Cmax_{,ss}$, $AUC_{\tau,ss}$, C_{trough} of canagliflozin on Day 7
DIA1030	Single and Multiple dose PK/PD Study in healthy subjects	27	PBO 50mg QD 100mg QD 300mg QD	$Cmax_{,ss}$, $AUC_{\tau,ss}$ of canagliflozin, M5, and M7 on Days 1 and 9
DIA1032	Assess the Steady-State PK/ PD and Safety of Once-Daily Versus Twice-Daily Dosing in healthy subjects	24	50mg BID 100mg QD 150mg BID	$Cmax_{,ss}$, $AUC_{\tau,ss}$, C_{trough} of canagliflozin on Day 5
DIA1034	DDI with HCTZ in healthy subjects	30	300mg QD	$Cmax_{,ss}$, $AUC_{\tau,ss}$, C_{trough} of canagliflozin on Day 7
DIA1048	DDI Probenecid on the Multiple-Dose Canagliflozin in Healthy Subjects	14	300mg QD	$Cmax_{,ss}$, $AUC_{\tau,ss}$, C_{trough} of canagliflozin on Day 14
Phase 2				
DIA2001	Metformin Add-on in patients with T2DM	364	PBO 50mg QD 100mg QD 300mg QD 300mg BID	$Cmax_{,ss}$, $AUC_{\tau,ss}$, C_{trough} of canagliflozin, M5, and M7 at Weeks 3, 6, & 12
Phase 3				
DIA3005	Monotherapy vs. PBO in patients with T2DM	678	100mg QD 300mg QD	C_{trough} of canagliflozin at Weeks 6, 12, & 26
DIA3009	Add-on to Met vs. glimepiride in patients with T2DM	1281	100mg QD 300mg QD	C_{trough} of canagliflozin at Weeks 8 and 52

Genotyping was performed in phase 1 and 2 trials for the single nucleotide polymorphisms (SNPs) as shown in table 2. In the phase 3 trials, DIA3005 and DIA3009, subjects were only genotyped for the *UGT1A9**3 variant.

Table 2. Genotyped SNPs

Allele	Reference	Variant	Remarks	Functional consequences
UGT1A9				
UGT1A9 -2152 C>T	C	T	H5 or H13 = (-275T>A and -2152C>T)	increased expression
UGT1A9 -275 T>A	T	A		
UGT1A9*3	T	C	M33T	substrate dependent impact
UGT1A9*5	G	A	D256N	decreased activity
UGT2B4				
UGT2B4*2	T	A	D458E	unknown
UGT2B4 rs1080755	A	G		increased expression

Source: JNJ-28431754 – Meta-Analysis page 10

*Comment: This review focuses on UGT1A9*3 effects on C_{trough} given the small number of variant carriers available for other exploratory analyses.*

3 Key Questions and Summary of Findings

3.1 Are differences in canagliflozin exposure resulting from polymorphisms in the gene encoding *UGT1A9* clinically relevant?

No. The effect of UGT1A9 genotype is small and while exposures are higher on average in variant carriers, the concentrations still fall within the range of exposures observed in subjects without UGT1A9 variants.

3.1.1 Applicant's analysis

The frequency of *UGT1A9*3 carriage (i.e., *1/*3) was 4% in white subjects (n=477) and 2.3% in Hispanic or Latino subjects (n=88); no variants were detected in Black/African-American subjects (n=44), Asian subjects (n=63), American Indian/Alaskan Native subjects (n=1), or other subjects (n=59).

*Comment: UGT1A9*3 frequencies in the white population are consistent with previously reported genotype frequencies in Caucasians (Villeneuve et al.; PMID 12944498). No variant homozygotes were enrolled.*

The applicant's primary analysis focused on dose-normalized canagliflozin plasma trough concentrations (C_{trough}). As shown below, C_{trough} were 80.7% higher in subjects carrying the *UGT1A9*3 allele than in non-carriers.

Table 3. Dose-normalized (100mg) canagliflozin plasma trough concentrations, (ng/ml)(C_{trough})

*UGT1A9*3* Carrier	N(%)	Geometric Mean	95% CI for Geometric Means	Ratio of Geometric Means	5th Percentile	Median	95th Percentile
No (**1/*1*)	711 (97.13)	104.47	(98-111.37)		30.87	100.67	493.33
Yes (**1/*3*)	21 (2.87)	188.76	(146.46-243.28)	1.81	107.00	183.00	456.67

(Studies included : 28431754DIA1007, DIA1023, DIA1028, DIA1030, DIA1032, DIA1034, DIA1048, DIA2001, DIA3005 and DIA3009)

Source: JNJ-28431754 - Meta-Analysis table 3

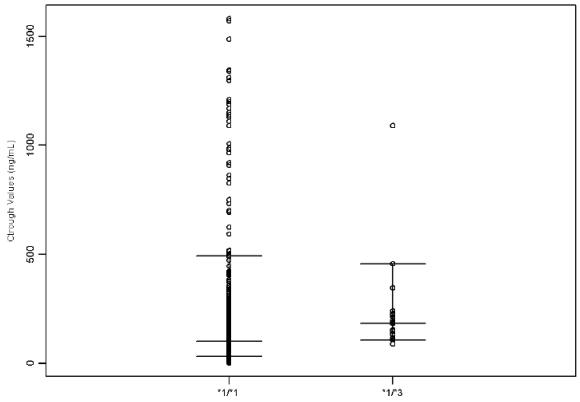


Figure 1.

Source: JNJ-28431754 - Meta-Analysis figure 1

*Comment: While canagliflozin concentrations were higher on average in subjects with the *1/*3 genotype, the observed values were all within the range of exposures observed in subjects with the *1/*1 genotype. The cause for the apparent outlying concentration in one of the *1/*3 subjects is unknown.*

In the applicant's additional exploratory analyses of other PK endpoints, dose-normalized $AUC_{\tau,ss}$ and $C_{max,ss}$ for canagliflozin were approximately 45% and 11% higher, respectively, in subjects carrying the *UGT1A9*3* allele relative to the mean concentrations in subjects without this variation.

Comment: Only 4 variant carriers were available for this analysis thereby limiting any conclusions.

In the applicant's population PK analyses considering other covariates, the applicant found that subjects carrying the *UGT1A9**3 allele had a 26% higher exposure (median dose-normalized AUC) vs. subjects with the *UGT1A9**1/*1. *UGT1A9* polymorphism was a statistically significant predictor of clearance in the population PK model, along with eGFR and dose.

Table 4. Dose-normalized (100 mg) canagliflozin geometric mean AUC values (ug.h/ml) by genotype

UGT1A9 genotype			Ratio
UGT1A9*1/*1 n=700	UGT1A9*1/*3 n=21	No genotype information n=895	
7.32 (4.59-12.2)	9.24 (7.48-13.8)	7.53 (4.89-13.2)	1.26 (1.08-1.44)

Source: JNJ-28431754 POP PK Report table 12

*Comment: The findings with AUC are consistent with C_{trough}, albeit of lower magnitude when considered with other factors including dose and eGFR. UGT1A9*3 genotype was not included in the final population PK analysis because of the low frequency and small effect.*

3.1.2 Reviewer's analysis

The sponsor's analyses based on the pharmacogenetics dataset were confirmed (\\cdsesub5\EVSPROD\NDA204042\\0000\m5\datasets\pop-pk-pgx\analysis\legacy\datasets\ ugtpk.xpt). Bivariate regression showed that *UGT1A9* genotype explained <5% of the variability in canagliflozin C_{trough}. While 53% of subjects carrying the *3 allele had exposures in the highest quartile, these subjects only represented 6.1% of all subjects in this range, suggesting limited predictive utility.

UGTB4 genotype did not have any effect on canagliflozin C_{trough} among the 291 subjects with data available, with or without stratification by *UGT1A9* genotype (not shown).

4 Summary and Conclusions

The UGT1A9*3 polymorphism is present in less than 5% of most ethnic groups. Compared to noncarriers, carriers of the *UGT1A9*3 allele exhibit higher plasma canagliflozin trough concentrations on average. However, canagliflozin exposures in this subgroup are within the range of exposures observed in noncarriers, and the *1/*3 genotype accounts for little of the overall variability in canagliflozin C_{trough}.

5 Recommendations

*UGT1A9*1/*3 genotype is associated with higher canagliflozin concentrations (C_{trough}) on average but it does not appear to be a robust or unique predictor of higher exposure. The genotype frequency of the *UGT1A9*3 occurs in less than 5% of Caucasians and is generally not identified in other races. The effect of the increased exposure on the primary efficacy outcome is likely to be of limited clinical relevance because of the small effect size. No additional action is indicated.

5.1 Post-marketing studies

None

5.2 Label Recommendations

None

4.2 Pharmacometric Review

4.2 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	204042
Submission Number (Date)	May 31, 2012
Compound (Dosing regimen)	Canagliflozin Immediate Release Tablets: 100 mg and 300 mg
Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Clinical Division	DMEP
Primary PM Reviewer	Manoj Khurana, Ph.D.
Secondary PM Reviewer	Anshu Marathe, Ph.D.
PM Team Leader	Nitin Mehrotra, Ph.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there dose-response for effectiveness for Canagliflozin?

Yes, the dose-response is evident among 100 mg and 300 mg QD Canagliflozin treatment regimens based on efficacy data. The time-profile for the LS mean change from baseline in HbA1c for one of the Phase 3 trial (Monotherapy trial DIA3005) is shown in Figure 1 below. A clear separation in mean HbA1c reduction from baseline over time profile was observed between the two active treatment arms (Canagliflozin; 100 mg and 300 mg) and the placebo group (Figure 1). The HbA1c reduction appeared to reach plateau by Week 26. Similar results were evident from the add-on therapy trials (See Appendix 4.1 Figure 21).

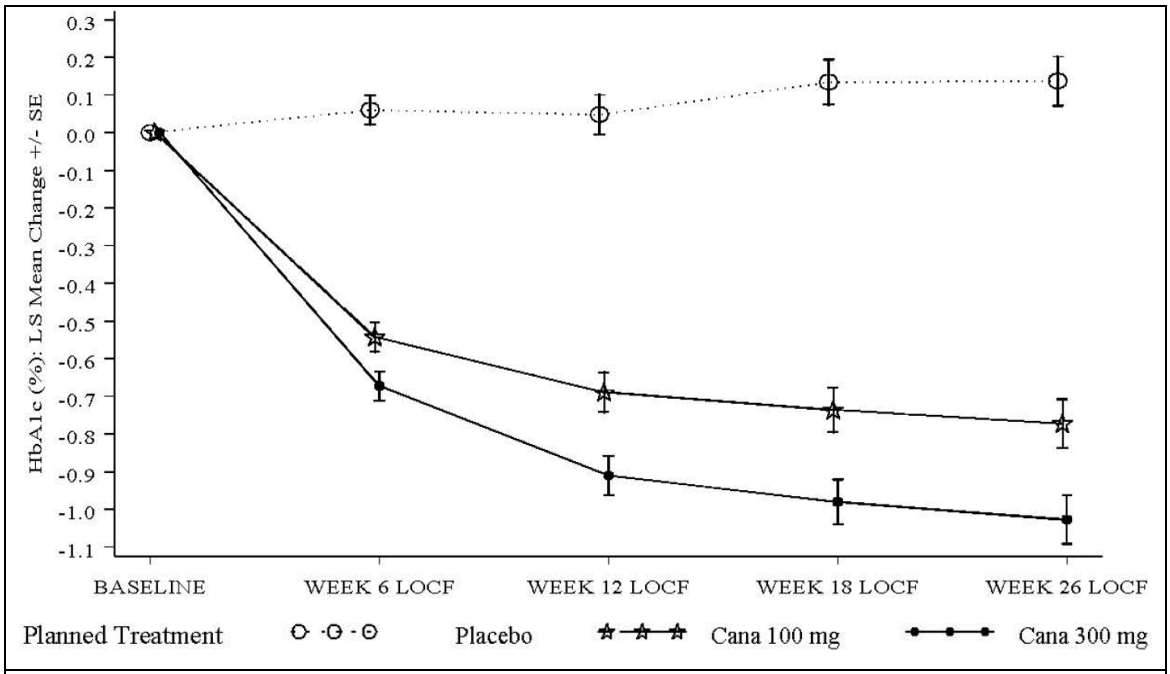
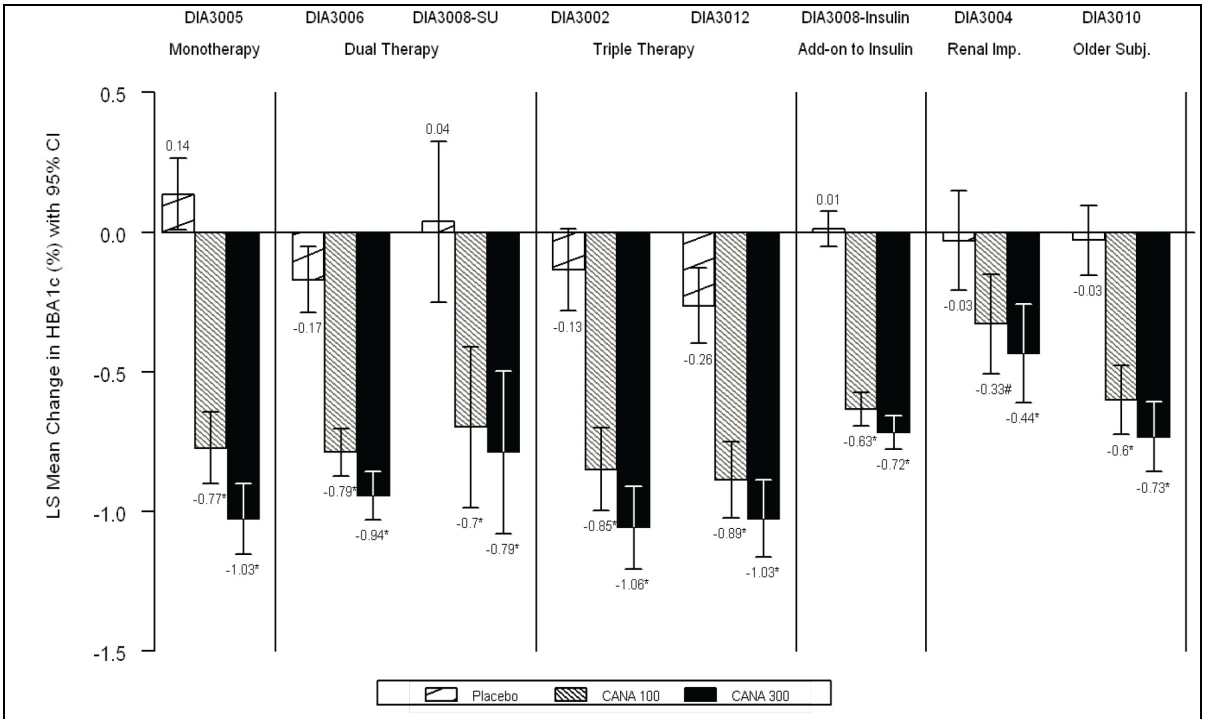


Figure 1: Time-profiles for mean (±SE) change from baseline in HbA1c in Phase 3 monotherapy trial DIA3005.
[*Source: Sponsor's Figure 4 in DIA3005 Study Report, Page 85]*

From sponsor's statistical analysis results, there is an evidence of dose-response relationship for effectiveness. The Phase 3 monotherapy and add-on therapy trials demonstrated a dose-dependant decrease in HbA1c, the primary efficacy end-point, in placebo-controlled trials (see Figure 2).



* Statistically significant (p<0.001) vs. placebo based on the ANCOVA models from individual studies.

CANA = canagliflozin, CI = confidence interval, Imp = impairment, ISE = Integrated Summary of Efficacy, LS = leastsquares, LOCF = last observation carried forward, mITT = modified Intent-to-Treat, SU = sulfonylurea, Subj = subjects.

Figure 2: Least Squares Mean Changes from Baseline in HbA1c (%) at Primary Assessment Time-point-LOCF: Study-by-Study Comparison (ISE Phase 3 Studies: Modified Intent-to-Treat Analysis Set). [*Source: Sponsor's Figure 3-1 in Summary of Clinical Efficacy, Section 3.2.1, Page 52]*

Note: As per the sponsor's analysis plan mITT set includes all randomized subjects who took at least one dose of double-blind study medication, LOCF: all efficacy data after rescue medication was censored, and the last post-baseline (i.e., after initiation of double-blind study medication) value prior to the time of rescue was carried forward.

Results from the Monotherapy Trial: At week 26, the placebo adjusted LS Mean change from baseline in HbA1c is numerically higher for the 300 mg QD dose group (-1.16) compared to the 100 mg QD dose group (-0.91) in DIA3005 trial. The placebo adjusted proportion of subjects who achieved target HbA1c levels of <7.0% by Week 26 was also higher for the 300 mg QD dose group (41.7%) compared to the 100 mg QD dose group (23.9%) in DIA3005 trial.

Results from the Add-on therapy Trials: Similar to the monotherapy trial, in the dual therapy trial DIA3006 (Add-on to Metformin versus placebo), at week 26, the placebo adjusted LS mean change from baseline in HbA1c was numerically higher for the 300 mg QD dose group (-0.77) compared to the 100 mg QD dose group (-0.62). The placebo adjusted proportion of subjects who achieved target HbA1c levels of <7.0% by Week 26 was also numerically higher for the 300 mg QD dose group (27.9%) compared to the 100 mg QD dose group (15.6%) in the trial DIA3006.

In another dual therapy trial DIA3009 (Add-on to Metformin versus Glimepiride), at week 52, the LS mean change from baseline in HbA1c was numerically higher, although little, for the 300 mg QD dose group (-0.93) when compared to the 100 mg QD dose group (-0.82). The 100 mg QD group response was similar in magnitude to the response for glimepiride arm (-0.81). The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 26 was numerically higher for the 300 mg QD dose group (60.1%) compared to the 100 mg QD dose group (53.6%), though similar to glimepiride (55.8%).

The dose-response was also evident from the add-on trials involving triple therapy. In trial DIA3002 (Add-on to metformin and sulfonylurea (SU)), at week 26, the placebo adjusted LS mean change from baseline in HbA1c was numerically higher for the 300 mg QD dose group (-0.92) compared to the 100 mg QD dose group (-0.71). The placebo adjusted proportion of subjects who achieved target HbA1c levels of <7.0% by Week 26 was numerically higher for the 300 mg QD dose group (38.6%) compared to the 100 mg QD dose group (25.2%).

In trial DIA3012 (Add-on to metformin and pioglitazone), at week 26, the placebo adjusted LS mean change from baseline in HbA1c was numerically higher, although little, for the 300 mg QD dose group (-0.76) compared to the 100 mg QD dose group (-0.62). The placebo adjusted proportion of subjects who achieved target HbA1c levels of <7.0% by Week 26 was numerically higher for the 300 mg QD dose group (31.8%) compared to the 100 mg QD dose group (14.4%).

In trial DIA3008 sub-study (Add-on to Insulin), at week 26, the placebo adjusted LS mean change from baseline in HbA1c was numerically higher, although little, for the 300 mg QD dose group (-0.73) compared to the 100 mg QD dose group (-0.65). The placebo adjusted proportion of subjects who achieved target HbA1c levels of <7.0% by Week 26 was numerically higher for the 300 mg QD dose group (17.0%) compared to the 100 mg QD dose group (12.1%).

Thus based on efficacy data, the dose-response is evident among 100 mg and 300 mg QD Canagliflozin treatment regimens. From efficacy perspective, the dose-response data suggests that the use of 300 mg QD dose of Canagliflozin, is more efficacious than 100 mg QD, when administered as monotherapy or as add-on therapy.

1.1.2 Is there impact of renal impairment on the efficacy of canagliflozin?

Yes, the evaluation of impact of renal function on Canagliflozin demonstrate that:

- Consistent with the known mechanism of action of canagliflozin, there appears to be a lower reduction in HbA1c levels with increasing degree of renal impairment in subjects with type 2 diabetes. The reduction in HbA1c from baseline in subjects with moderate renal impairment (DIA3004) was of lower magnitude (approximately half) when compared to the magnitude observed in type 2 diabetic subjects majority with normal renal function or with mild renal impairment in trial DIA3005 or add-on dual therapy trials DIA3006 and DIA3008 (Figure 2).
- Even though the mean response is low in subjects with mild renal impairment compared to subjects with normal renal function, efficacy of Canagliflozin is preserved in these patients.

- In subjects with moderate renal impairment a trend of modest, dose-dependant decrease in HbA1c is observed following 26 weeks treatment with canagliflozin (Figure 1); however, when evaluated based on baseline renal function this trend is primarily driven by subjects with eGFR $\geq$ 40 mL/min/1.73m^2 (Figure 5). Canagliflozin doers not appear to be efficacious in type 2 diabetic patients with eGFR < 40 mL/min/1.73m^2.

Mechanistic basis of lower efficacy in patients with impaired renal function:

Lower efficacy in patients with impaired renal function is consistent with the primary mechanism of action of Canagliflozin [sodium glucose co-transporter 2 (SGLT2) inhibition in the proximal renal tubules], which is dependant on the functional capacity of the renal filtration. Re-absorption of virtually all filtered glucose occurs up to plasma glucose (PG) levels of approximately 10 mmol/L (200 mg/dL), designated as the renal threshold for glucose re-absorption (RT_G). Inhibition of SGLT2 by Canagliflozin resulted in lowering of the RT_G from ~215 mg/dL at baseline to 43 mg/dL at 100 mg dose in subjects with type 2 diabetes mellitus[1], see Figure 3a). This results in increased urinary glucose excretion, thus reducing hyperglycemia.

Following administration of Canagliflozin in subjects with reduced capacity of renal filtration, urinary glucose excretion (UGE) declined based on the degree of renal impairment (Figure 3b), as expected mechanistically.

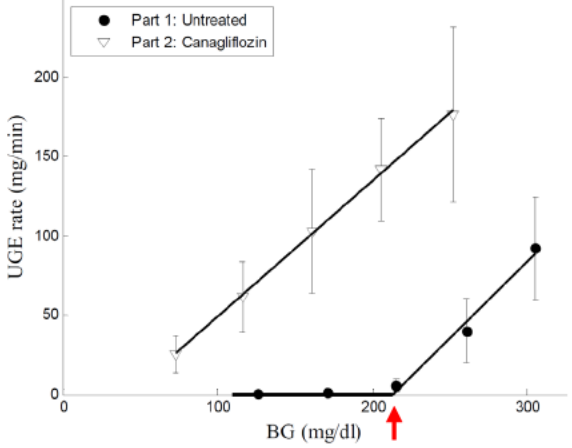


Figure 3a: Relationship Between Blood Glucose Concentration and UGE Rate During the Stepwise Hyperglycemic Clamps after canagliflozin treatment (100 mg single oral dose)[RT_G by red arrow][1]

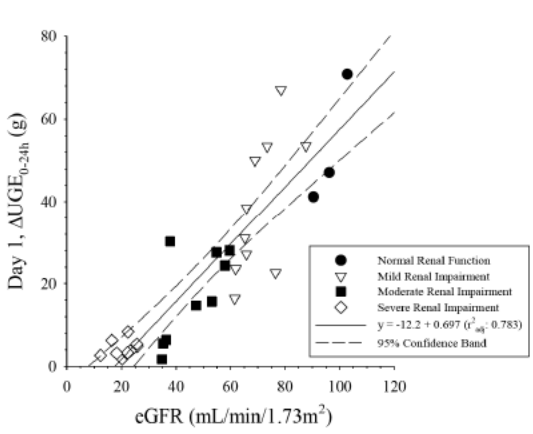


Figure 3b: UGE0-24h changes from baseline (Day -1) versus eGFR in subjects with varying degrees of renal function after single 200 mg oral dose of canagliflozin[2]

Observed clinical trial data indicating lower efficacy in moderate renal impairment:

The sponsor conducted a dedicated efficacy and safety evaluation (Trial DIA3004) in subjects with type 2 diabetes mellitus who had moderate renal impairment. Subjects on

[1] Study Report DIA1025 Page 42
[2] Source: Sponsor's clinical study report addendum DIA1003

stable anti-hyperglycemic agent (AHA) therapy [including SUs, pioglitazone, DPP-4 inhibitors, alpha-glucosidase inhibitor (AGI), GLP-1 analogue, pramlintide, or insulin] were randomly assigned to Canagliflozin 100 mg QD or 300 mg QD or placebo treatment.

Figure 4 below shows the time-profile for the LS mean change from baseline in HbA1c for trial DIA3004. A slight dose-dependent separation in mean HbA1c reduction from baseline over time profile was evident between the two active treatment arms (Canagliflozin; 100 mg and 300 mg) and the placebo group (Figure 4).

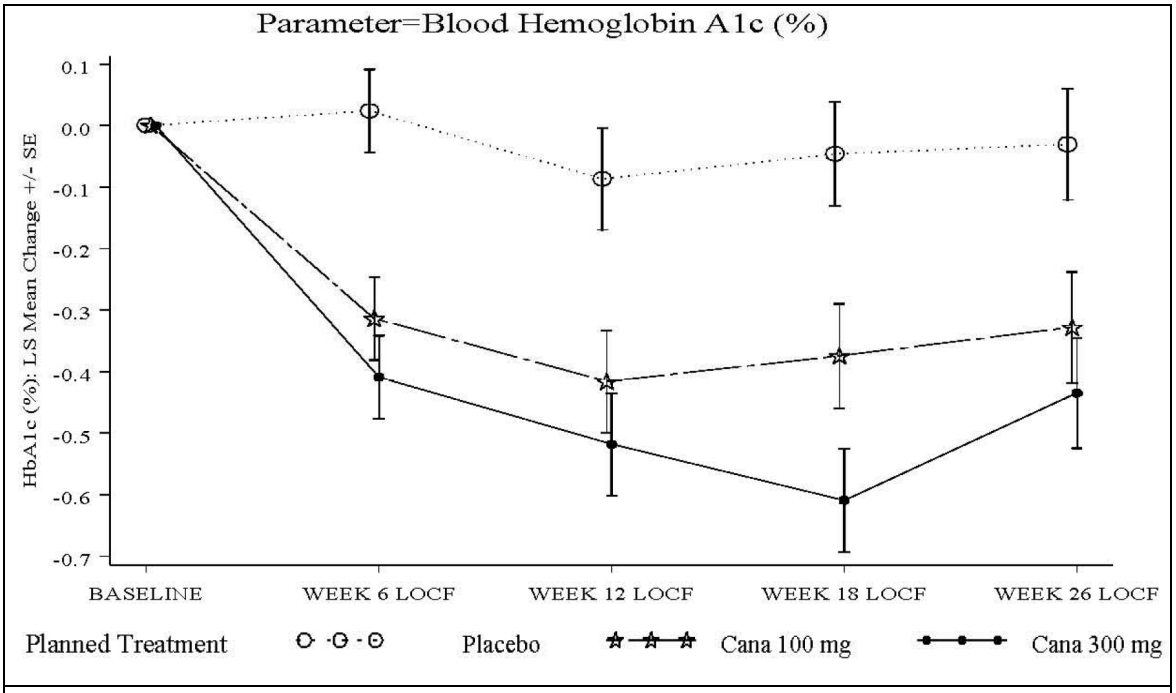


Figure 4: Time-profiles for mean (±SE) change from baseline in HbA1c in moderate renal impairment phase 3 trial DIA3004
[*Source: Sponsor's Figure 4 in DIA3004 Study Report, Page 80]*

The LS mean change in HbA1c in subjects with moderate renal impairment (DIA3004) was lower than placebo (-0.03) for both 100 mg QD and 300 mg QD dose groups, LS mean HbA1c reduction of -0.33 and -0.44, respectively (See Figure 4 and Figure 1). However, the overall magnitude of response was low *per se*, as well as in comparison to the response observed in monotherapy trial DIA3005 (LS mean HbA1c reduction from baseline was -0.77 and -1.03 for 100 mg QD and 300 mg QD, respectively) where majority of subjects were with normal renal function or mild renal impairment. Since the use of stable AHA therapy was permitted in trial DIA3004, somewhat fair comparison of the efficacy response from this trial against that observed in dual therapy trials DIA3006 and DIA3008, also suggest a similar reduction in magnitude of response (See Figure 1). Proportion of subjects, who achieved target HbA1c levels of <7.0% by Week 26, was higher for the 300 mg QD dose group (32.6%) compared to the 100 mg QD dose group (27.3%) versus that observed with placebo (17.2%).

Analysis to explore efficacy within patients with moderate renal impairment:

A post-hoc analysis was also conducted for trial DIA3004 (trial conducted in patients with moderate renal impairment), evaluating efficacy in subgroups with an eGFR cut-off of 40 mL/min/1.73m^2 (i.e., the median eGFR value in trial 3004). Figure 5 describes the mean change in HbA1c from baseline to week 26 across treatment groups (placebo, canagliflozin 100 mg and 300 mg) and baseline renal function subcategories (eGFR < 40 and ≥ 40 mL/min/1.73m^2; this stratification is based on median eGFR value of 40 mL/min/1.73m^2 in this trial) in moderate renal impairment trial DIA3004. Overall, in subjects with moderate renal impairment a trend of modest, dose-dependant decrease in HbA1c is observed following 26 weeks treatment with canagliflozin; however, this trend is primarily driven by changes in HbA1c from baseline in subjects with eGFR ≥ 40 mL/min/1.73m^2. At week 26, magnitude of change in HbA1c from baseline in subjects with eGFR< 40 mL/min/1.73m^2 appears similar between placebo and treatment groups.

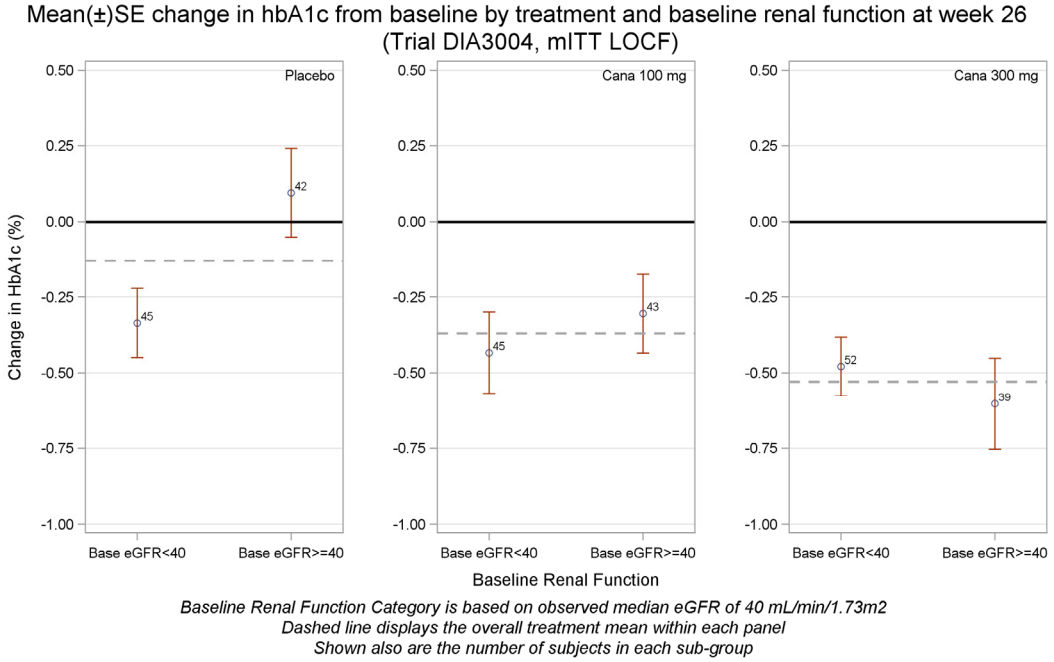


Figure 5: Change in HbA1c is affected by baseline renal function and treatment in type 2 diabetes mellitus subjects with moderate renal impairment (DIA3004)

As exploratory analysis, efficacy data was also evaluated graphically, based on the baseline renal function for pooled data from monotherapy and add-on Phase 3 trials. Figure 6 presents the overall trend for change in efficacy with severity of renal impairment, by treatment groups (placebo, canagliflozin 100 mg and 300 mg). Mean change in HbA1c from baseline to week 26 (end-point for most trials) is plotted versus the median of each baseline renal function subcategories (eGFR>100, 100>eGFR≥90, 90>eGFR≥75, 75>eGFR≥60, 60>eGFR≥45, eGFR<45 mL/min/1.73m^2). Overall, the data demonstrate a trend for reduced efficacy with decrease in eGFR.

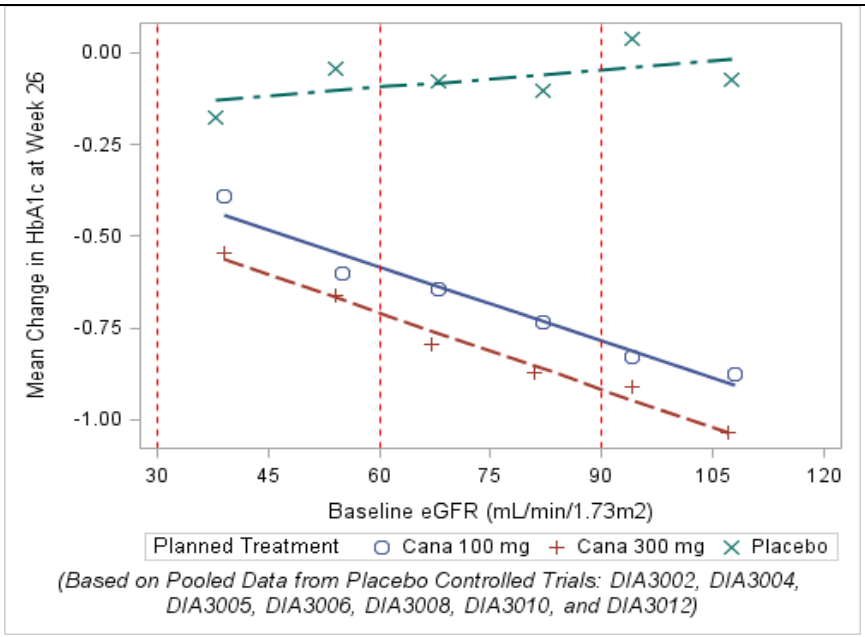


Figure 6: Exploratory graphical analysis shows a trend for decrease in Canagliflozin efficacy (change in HbA1c) with the degree of renal impairment for both 100 mg QD and 300 mg QD treatment in pooled placebo controlled phase 3 trials data in type 2 diabetes mellitus subjects. Note that except DIA3005 trial, all other trials were add-on therapy trials on background use of stable anti-hyperglycemic therapy (dual or triple therapy).

1.1.3 What is the dose-safety relationship of Canagliflozin?

Dose-safety analysis revealed that:

- Canagliflozin decreased eGFR from baseline in a dose-dependent manner. This decrease in eGFR was also dependent on the baseline renal function. On average, the decline in eGFR appeared to regress over time towards baseline.
- Among moderate renal impairment subjects, the proportion of subjects with >30% decline in eGFR increase in dose and baseline renal function dependent manner when evaluated for eGFR>=40 and eGFR<40 subgroups. Comparison of week 3 and week 26 data suggest that this adverse reation of canagliflozin seems to improve at least in the eGFR>=40 group.
- In all canagliflozin treated subjects, the changes in electrolytes and renal safety markers also increase in dose dependant manner although, majority of them regress over trial duration.

Dose safety of Canagliflozin was evaluated with respect to impact on renal function, changes in relevant safety laboratory markers, and volume depletion adverse events.

Canagliflozin Impact on Renal Function:

Canagliflozin lowered the eGFR from baseline in both, dose and baseline renal function dependent manner. Effect of canagliflozin on renal function was evaluated based on

longitudinal change from baseline in eGFR, and by evaluating the reduction in eGFR as a function of baseline renal function.

a. Longitudinal Change in eGFR following Treatment with Canagliflozin

Figure 7 shows the longitudinal change from baseline in eGFR by treatment for pooled placebo controlled trials (DS1: Trials DIA3002, DIA3005, DIA3006, and DIA3012) wherein, most of the patients were with normal renal function or mild renal impairment.

Based on the pooled placebo controlled phase 3 trial data, on average the eGFR decrease from baseline was maximal (approximately -4 and -5 mL/min/1.73m^2, respectively for 100 mg and 300 mg dose of Canagliflozin) at the first observation of week 6 after initiation of the treatment. The eGFR values then trended towards improvement but did not return to the baseline by the time of primary end-point assessment at week 26, in most of the trials.

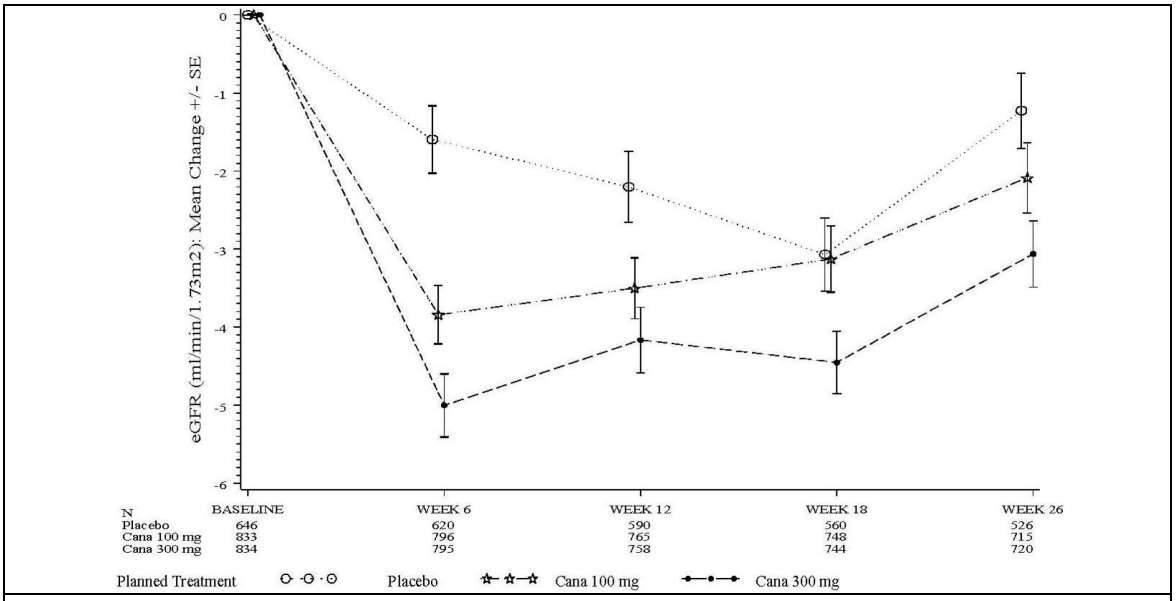


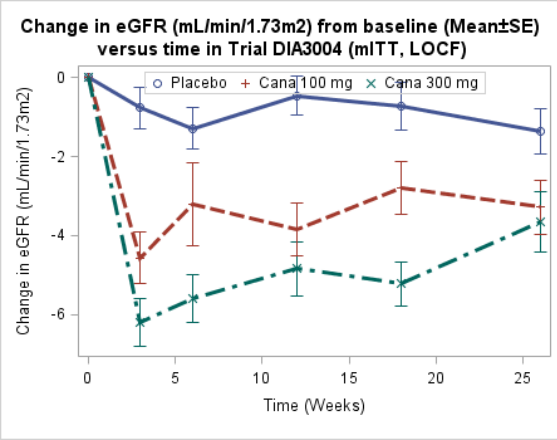
Figure 7: Mean change (+/-SE) in eGFR (mL/min/1.73m2) from baseline over time (ISS Phase 3 Placebo-Controlled Studies Dataset DS1: Safety Analysis Set). ***[Source: Summary of Clinical Safety, Figure 17, Page 242]***

The impact of canagliflozin on longitudinal change in renal function was evaluated in two specific populations of interest from a safety perspective: subjects with moderate renal impairment in Trial DIA3004 (already compromised renal function), and elderly population in Trial DIA3010 (fragile due to age related changes in physiological functions).

Figure 8 shows the longitudinal change from baseline in eGFR by treatment for type 2 diabetic subjects who have moderate renal impairment (Trial DIA3004), and elderly patients (Trial DIA3010). In moderate renal impairment subjects, on average, the eGFR decrease from baseline was maximal (-4.6 and -6.2 mL/min/1.73m^2, respectively for 100 mg and 300 mg dose of Canagliflozin) at the first observation of week 3 after initiation of the treatment.

Similar dose dependent decline in renal function was also observed for the trial in elderly subjects (DIA 3010) with eGFR decline of -4.4 and -5.9 mL/min/1.73m^2 at week 6 for 100 mg and 300 mg dose, respectively although the renal function appeared to return towards baseline after week 6.

A. Trial – DIA3004 (T2DM with Moderate Renal Impairment)



B. Trial – DIA3010 (Elderly T2DM with Normal Renal Function, Mild, or Moderate Renal Impairment)

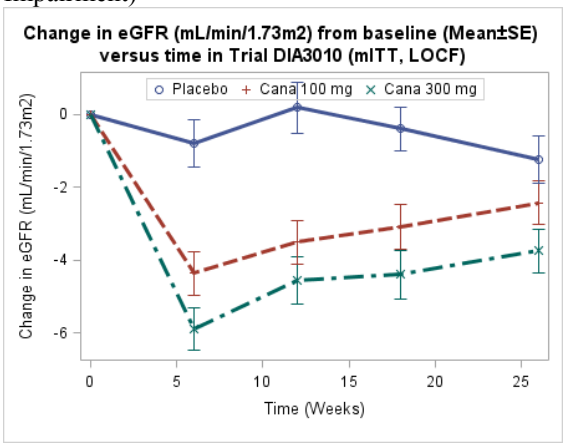


Figure 8: Canagliflozin reduces eGFR fro baseline both in type 2 diabetic subjects who have moderate renal impairment, and elderly type 2 diabetic subjects with normal renal function or mild/moderate renal impairment.

The baseline demographic data showed that there was substantial overlap with regards to age between trial DIA3004 (60-70% subjects ≥ 65 years) and trial DIA3010 (~40% ≥ 65 years and ~60% subjects between 55 and 65 years). However, with regards to moderate renal impairment, only 11-13 % subjects in trial DIA3010 had moderate renal impairment as opposed to 100% subjects in trial DIA3004. Therefore, further post-hoc analysis for change in eGFR based on baseline renal function following treatment with canagliflozin was focused primarily on the results from DIA3004 trial as presented below.

b. Analysis for Change in eGFR Based on Baseline Renal Function Following Treatment with Canagliflozin

Similar to efficacy, a post-hoc analysis was also conducted to compare the safety in eGFR<40 mL/min/1.73m^2 and eGFR>=40 mL/min/1.73m^2 subgroups.

Change in eGFR in the moderate renal impairment was further evaluated by baseline renal function subgroups (eGFR< 40 and ≥ 40 mL/min/1.73m^2; stratified by median eGFR of 40 mL/min/1.73m^2) at week 3, the point of maximal change in trial DIA3004 (Figure 7). Note that, unlike efficacy, which was compared at week 26 between baseline renal function subgroups (Figure 5), the change in eGFR at week 3 or 6 was selected for comparison. Maximum decline in eGFR from baseline was observed at first assessment on Week 3 following treatment with Canagliflozin in DIA3004 trial and at Week 6 for other Phase 3 trials.

In trial DIA3004, a trend of dose-dependent decrease in renal function (i.e., eGFR) was observed for both baseline eGFR< 40 and ≥ 40 mL/min/1.73m^2 subgroups, with relatively higher mean decline in eGFR for 300 mg dose groups than 100 mg dose group.

However, on an average, the renal function appeared to recover following longer treatment with Canagliflozin, with relatively low differences for change in eGFR between placebo and treatment groups at week 26 (Figure 8).

Further, Figure 9 shows that mean decrease in eGFR was greater for patients with higher baseline eGFR (i.e., ≥ 40 mL/min/1.73m^2) than in patients with low baseline eGFR (i.e., <40 mL/min/1.73m^2). Similar baseline renal function dependent decline in renal function was also seen in elderly patients (Figure 25 in Appendix 4.3).

Overall data from trial DIA3004 and DIA3010 suggest that mean decline in eGFR was dependent on both dose and baseline eGFR.

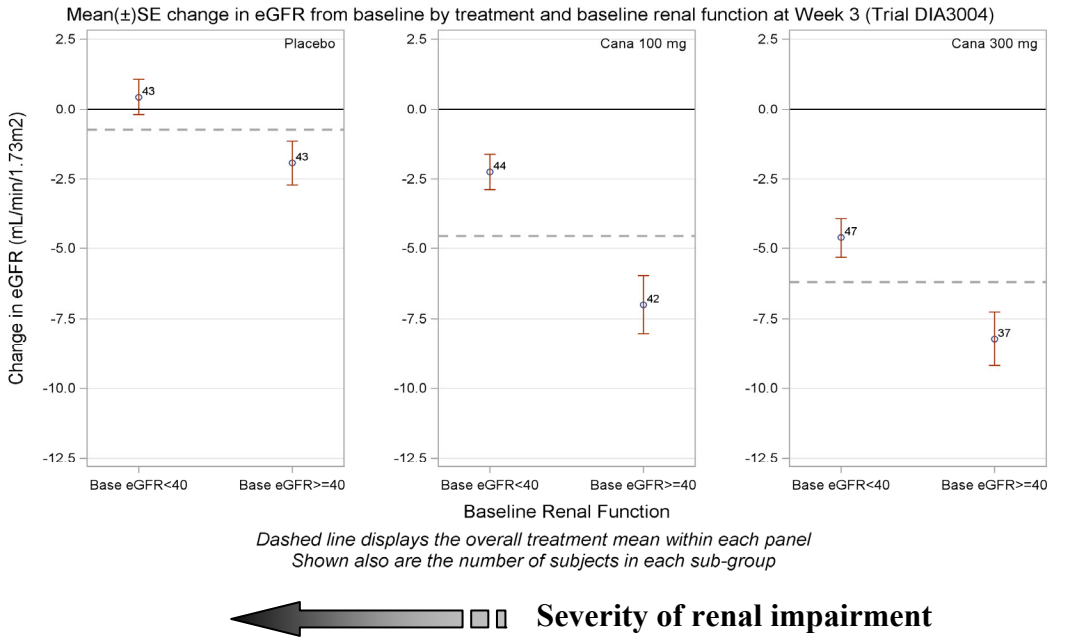
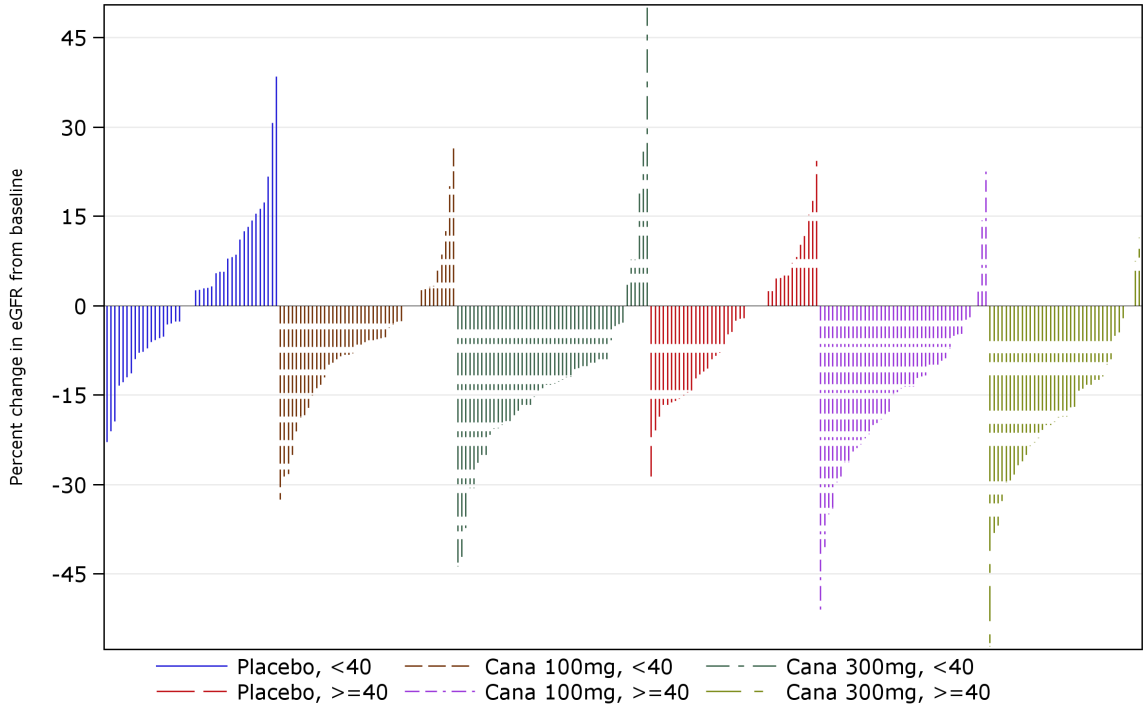


Figure 9: Change in eGFR from baseline by treatment and baseline renal function (eGFR) [DIA3004; mITT, Week 3]

The needle plot in Figure 10 compares the percent decline in eGFR between placebo and canagliflozin treatment groups at week 3 and week 26 based on baseline renal function (eGFR<40 vs. >=40 mL/min/1.73m^2) in patients with moderate renal impairment (Trial DIA3004).

- In eGFR<40 group, more number of patients on canagliflozin treatment had decline in eGFR from baseline compared to placebo and the magnitude of decline was also higher than placebo. Similar differences between placebo and treatment groups were also observed for eGFR>=40 group.
- At week 3, comparison of eGFR<40 and eGFR>=40 groups show that both the magnitude of percent reduction in eGFR and number of subjects with decline in eGFR is higher for eGFR>=40 group (consistent with Figure 9).
- The decline in renal function (eGFR) appeared to regress over time (i.e., by week 26). Although, similar to week 3, a higher number of patients in treatment group had decline in eGFR compared to placebo, but on an average the magnitude of decline in eGFR was relatively low at week 26.

Week 3:



Week 26:

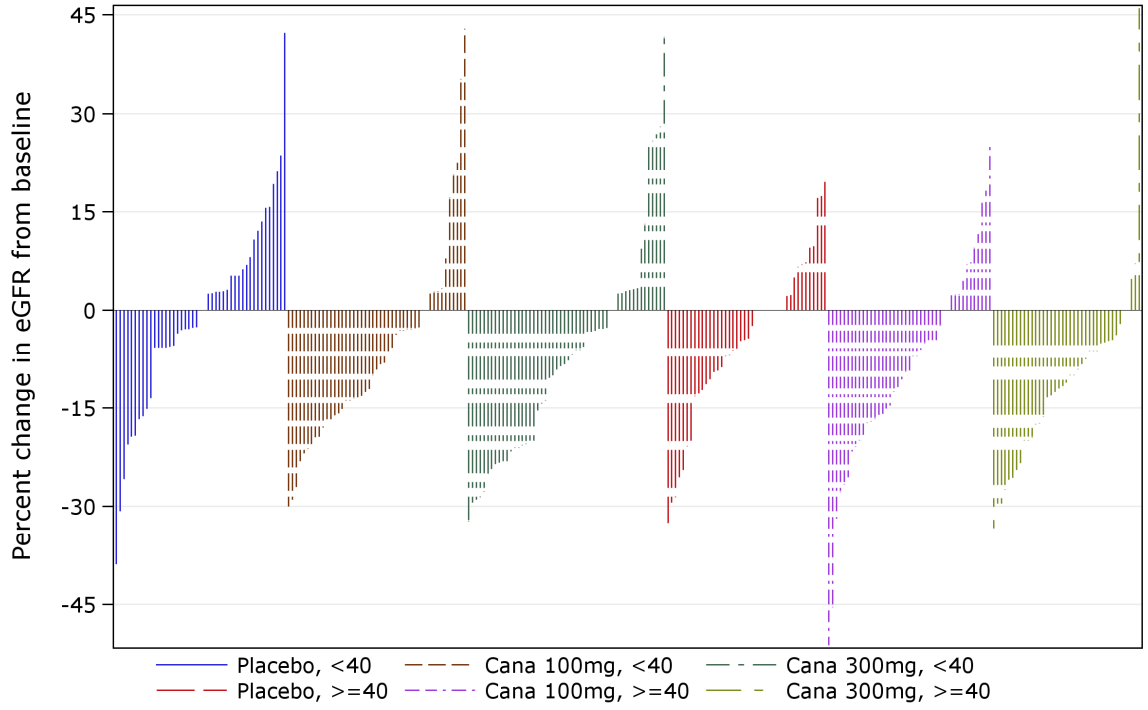


Figure 10: Needle plot comparing percent decline in eGFR in Placebo vs. Treatment groups based on baseline renal function category (Week 3 (top) and 26 (bottom) LOCF data DIA3004). Each vertical line represents one patient.

Patients with >30% and >50% decline in Renal Function (eGFR) from baseline at any time-point over treatment duration in Trial DIA3004

Although this analysis is limited by number of patients in each subgroup, the purpose is to indicate the trends. In eGFR>=40 mL/min/1.73m^2 group, percentage of patients with >30% reduction in eGFR from baseline (Table 1) were 10-12-fold higher with canagliflozin treatment compared to placebo. In eGFR<40 mL/min/1.73m^2 group, treatment with canagliflozin further increased the risk of reduction in eGFR by about 2-3-fold compared to placebo. This indicates that patients with moderate renal impairment, who are receiving canagliflozin, are more susceptible to decline in renal function in comparison to placebo.

Further, comparison of placebo groups in eGFR<40 mL/min/1.73m^2 and eGFR >=40 mL/min/1.73m^2 groups show that patients with more compromised renal function at baseline are at about 2.5 fold higher risk of further reduction (i.e., >30% reduction from baseline) in eGFR.

Greater than 30% reduction in eGFR for a patient with baseline eGFR of <40 mL/min/1.73m^2, may bring that patient into a severe renal impairment category, which will not only limit the use of canagliflozin but also other drugs which are only approved for moderate renal impairment and not for severe renal impairment.

However, the same reduction of 30% in eGFR in a patient with baseline eGFR of >=40 mL/min/1.73m^2 will likely keep that patient into moderate renal impairment category and thus not limit the use of canaglifozin or other approved treatments.

Table 1. Number of patients with >30% reduction in eGFR from baseline at any time point based on Trial DIA3004

>30% reduction in eGFR from baseline						
		eGFR <40			**eGFR >=40**	
	Placebo	**100 mg**	**300 mg**	**Placebo**	**100 mg**	**300 mg**
number of events	3	7	10	1	9	10
total patients	45	47	52	42	43	39
%	6.67	14.89	19.23	2.38	20.93	25.64

There were only 3 patients with > 50% decline in eGFR from baseline in Study DIA 3004. However, it is worth noting that all three cases were observed in patients receiving canagliflozin (Table 2).

Table 2. Number of patients with >50% reduction in eGFR from baseline at any time point based on Trial DIA3004

>50% reduction in eGFR from baseline						
		eGFR <40			eGFR >=40	
	Placebo	100 mg	300 mg	Placebo	100 mg	300 mg
number of events	0	0	1	0	1	1
total patients	45	47	52	42	43	39
%	0	0	1.92	0.00	2.33	2.56

Canagliflozin impact on safety related laboratory markers, renal related adverse events, and volume depletion adverse events:
Canagliflozin treatment results in dose-dependant increase in blood urea nitrogen, and serum electrolytes (magnesium, potassium, and phosphate), and incidences of volume depletion adverse events. The effect on hematocrit was similar for both 100 and 300 mg QD doses.

Patients with Renal Impairment Related Adverse Events

The percentage of patients with renal related adverse events was also evaluated from the pooled data set for patients with moderate renal impairment (combined data from studies DIA 3004, 3005, 3008, and 3010). Following terms were used in the database search: 'Acute prerenal failure' 'Azotaemia' 'Diabetic nephropathy' 'Nephritis' 'Nephropathy' 'Renal failure' 'Oliguria' 'Renal failure acute' 'Renal impairment' 'Renal tubular necrosis' 'Renal atrophy'.

- In eGFR>=40 mL/min/1.73m^2 group, we observe about a 2-fold increase in renal function related adverse events following treatment with canagliflozin compared to placebo (Table 3).

- Comparison of placebo groups in eGFR<40 and eGFR >=40 groups show about a 2 fold increase in renal function related adverse events in patients with more compromised renal function (i.e., eGFR<40). Infact, the % of renal function related adverse events in placebo with eGFR<40 are higher than that for eGFR >=40 patients receiving canagliflozin. This suggests that patients with eGFR<40 inherently may be at higher risk for renal function related adverse events.

- In eGFR<40 mL/min/1.73m^2 group, patients receiving canagliflozin had a comparable or higher risk of renal function related adverse events when compared to placebo.

- Comparison of renal function related adverse events between eGFR<40 and eGFR >=40 groups, show a relatively higher risk irrespective of placebo or canagliflozin treatment.

Table 3. Number of patients with renal function related adverse events based on pooled data from trials DIA 3004, 3005, 3008 and 3010 (DS2: Moderate renal impairment dataset)

Pooled data (DS2)						
		eGFR <40			eGFR >=40	
	Placebo	100 mg	300 mg	Placebo	100 mg	300 mg
number of events	4	6	4	7	11	12
total patients	67	70	72	316	272	297
%	5.97	8.57	5.56	2.22	4.04	4.04

Note: There were relatively small number of subjects in eGFR<40 category.

The effect of Canagliflozin on some of the key laboratory markers was evaluated from the Phase 3 Trials for DIA3004 and DIA3010 trials to weigh in the risk factors for these two specific populations (only those with notable change are shown here such as blood urea nitrogen, hematocrit, and electrolytes - serum magnesium, potassium, phosphate, and sodium). Further, more or less similar trends were evident in other phase 3 trials – monotherapy and add-on (data not shown). However, results in moderate renal impairment trial DIA3004 and elderly population trial DIA3010 are emphasized to highlight the benefit-risk profile of Canagliflozin in these two specific populations.

The time-profiles for mean (±SE) change from baseline in select laboratory markers-BUN and Hematocrit (Figure 10) and serum electrolytes (Figure 11), as observed in type 2 diabetes mellitus subjects with moderate renal impairment Phase 3 trial DIA3004, and elderly patients in DIA3010, are presented below. There was a dose dependent increase in serum blood urea nitrogen (Figure 11). Similarly, the dose dependent increase was evident for serum electrolytes (Figure 12).

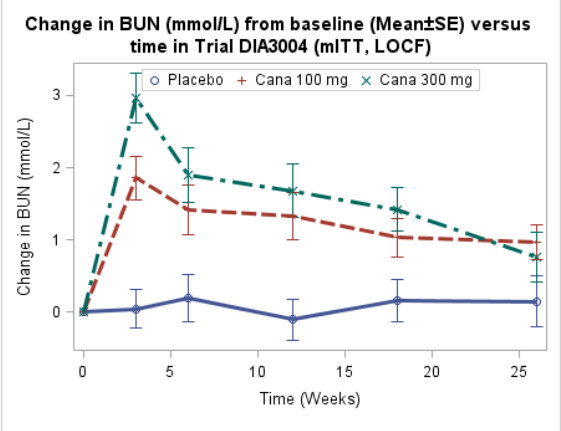
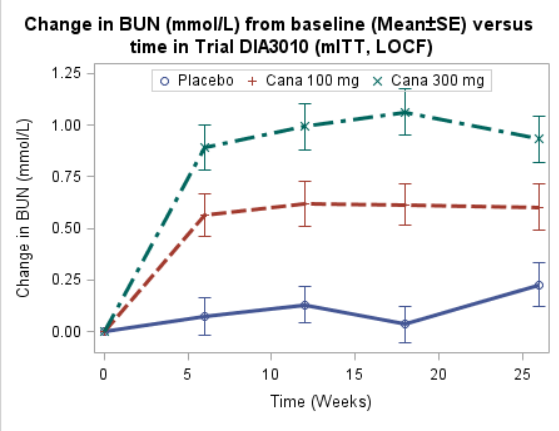
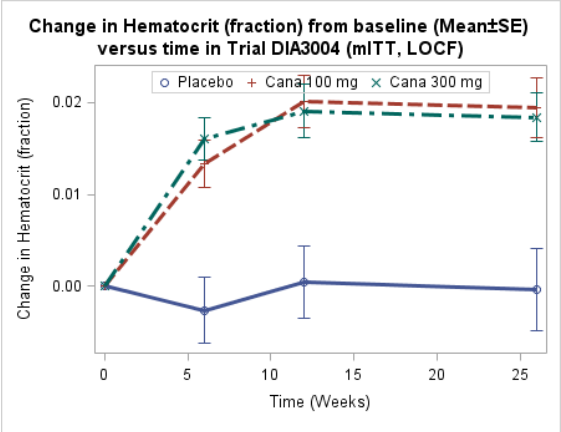
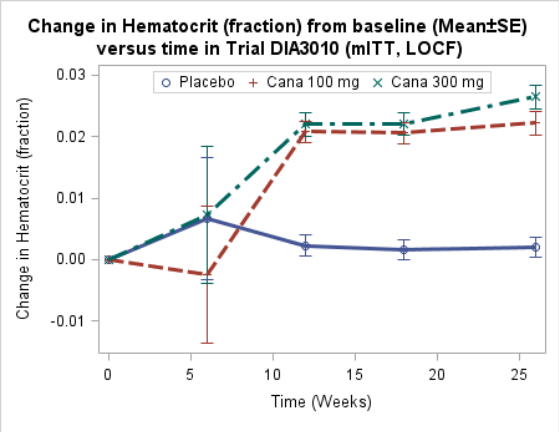
Moderate Renal Impairment (DIA3004)	Elderly (DIA 3010)
A. Serum Blood Urea Nitrogen (BUN)	**A. Serum Blood Urea Nitrogen (BUN)**
	
B. Hematocrit	**B. Hematocrit**
	

Figure 11: Time-profiles for mean (±SE) change from baseline in BUN and Hematocrit observed in type 2 diabetes mellitus subjects with moderate renal impairment Phase 3 trial DIA3004 and Elderly patients in DIA3010.

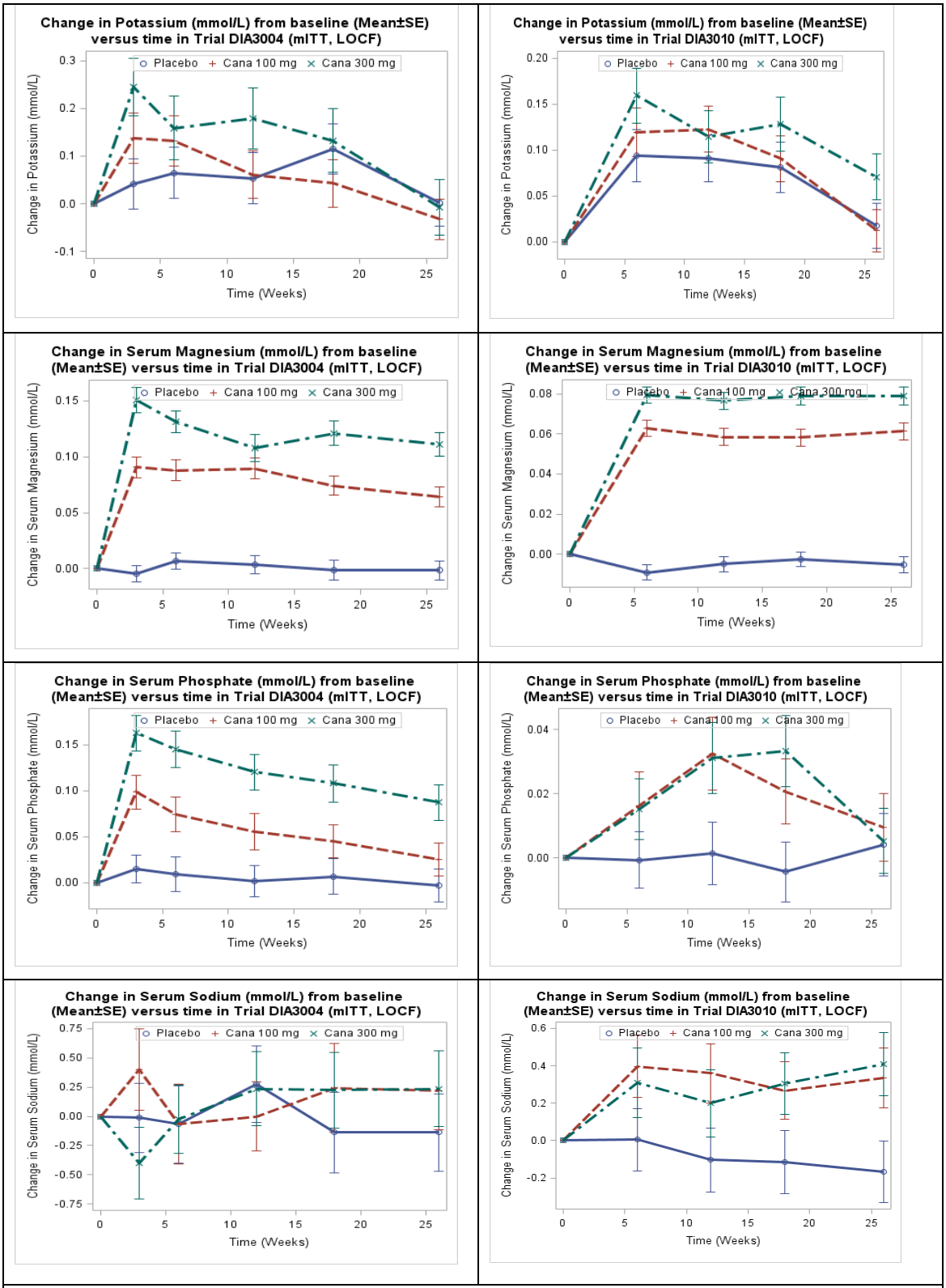


Figure 12: Time-profiles for mean (±SE) change from baseline in serum electrolytes observed in type 2 diabetes mellitus subjects with moderate renal impairment Phase 3 trial DIA3004 and Elderly patients in DIA3010.

Further, there was a trend for increasing proportion of subjects with adverse events related to volume depletion with increasing dose (Appendix 4.3 Table 8).

The proportion of subjects with adverse events (AEs) related to volume depletion were further increased, specifically in the presence of moderate renal impairment, age>=75, and concomitant use of loop diuretics (Figure 13), and this increase also appeared to be dose dependent.

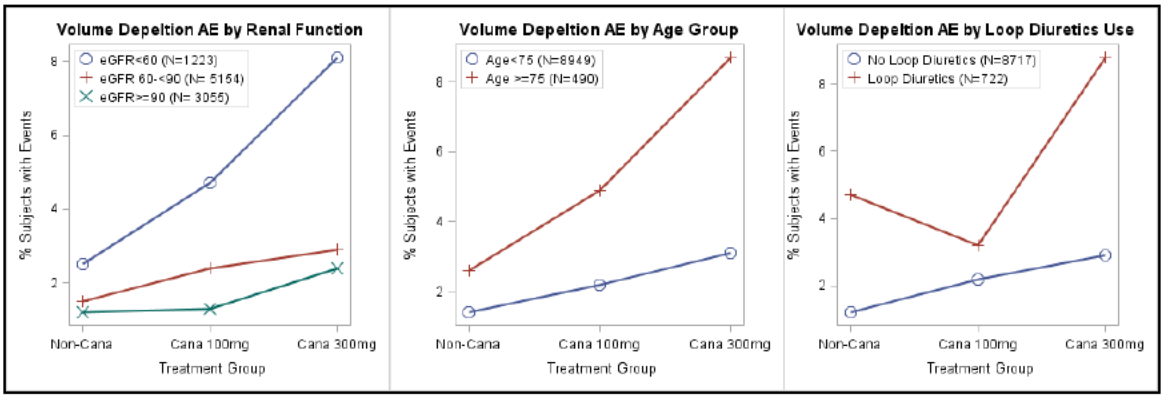


Figure 13: Increased incidence of volume depletion in moderate renal impairment, patients >=75 years, and with concomitant use of loop diuretics [Pooled Phase 3 broad data, See Table 8 in Appendix 4.3]

When evaluated for renal function and use of loop diuretics together, both moderate renal impairment and use of loop diuretics appeared to raise the incidence of volume depletion AE in independent manner with some additive effect in terms of number of AEs when both factors were present together (See Table 4 below). The dose dependent increase in proportion of subjects with AE was seen for all eGFR and loop diuretic use based categories.

Table 4: Proportion of Subjects with Volume Depletion Adverse Events by Use of loop diuretics and renal function - Regardless of Use of Rescue Medication (ISS Phase 3 Broad Dataset: Safety Analysis Set)

		Incidence[a]			
	% (n) in population[b]	Cana 100 mg % (n/N)	Cana 300 mg % (n/N)	Difference % (Cana 300 mg minus Cana 100 mg)	All Non-Cana % (n/N)
eGFR (mL/min/1.73m^2) and Use of Loop Diuretics Category at Baseline	N = 9432				
eGFR ≥60 and No Use of Loop Diuretics	82.5% (n=7784)	1.9% (50/2577)	2.4% (61/2528)	0.5%	1.2% (31/2679)
eGFR <60 and No Use of Loop Diuretics	9.8% (n=927)	4.7% (14/297)	7.2% (22/306)	2.5%	1.9% (6/324)
eGFR ≥60 and Use of Loop Diuretics	4.5% (n=425)	2.3% (3/130)	7.3% (11/151)	5.0%	4.9% (7/144)
eGFR <60 and Use of Loop Diuretics	3.1% (n=296)	4.7% (4/85)	11.1% (11/99)	6.4%	4.5% (5/112)

[a] Incidence of volume depletion adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP.

[b] Number of subjects in the Safety Analysis Set with the baseline characteristic.

Source: Sponsor's Table 90 in Summary of Clinical Safety, Page 238

1.1.4 Does the dose-response relationship for effectiveness and safety support the proposed doses of 100 mg QD and 300 mg QD in type 2 diabetes patients with normal renal function or mild renal impairment, with moderate renal impairment, in patients on loop diuretics and elderly patients?

- *Dosing in type 2 diabetic patients with normal renal function (eGFR > 90 mL/min/1.73 m^2) and mild renal impairment (eGFR = 60-90 mL/min/1.73 m^2):*
    - Benefit:

      Yes, the dose-response relationship, evident among 100 mg and 300 mg QD doses for reduction in HbA1c, supports the proposed doses of Canagliflozin as 100 mg once daily (QD) and 300 mg QD in this population, as an adjunct to diet and exercise to improve glycemic control. Reductions in HbA1c for monotherapy/dual therapy/triple therapy Phase 3 trials ranged from -0.77 % to -0.89 % and -79 % to -1.06 % for 100 mg QD and 300 mg QD dose, respectively. Note that most of the diabetic patients need combination therapies in order to get an optimal glycemic control and canagliflozin is also likely to be used in background of metformin or other antidiabetic therapies. The combination therapy trials that sponsor conducted for canagliflozin showed a modest incremental benefit (0.09 to 0.21% additional reductions in HbA1c) of using 300 mg QD as compared to the 100 mg QD. Even with lower mean response in comparison to subjects with normal renal function, efficacy of Canagliflozin was preserved in type 2 diabetes mellitus subjects with mild renal impairment with both 100 mg QD and 300 mg doses.

    - Risk:

      There are dose-dependent changes in the various adverse events - volume depletion related adverse events, renal function changes, and mineral and electrolyte changes. Most of the changes occurs early, i.e., within 3-6 weeks of initiating therapy, with higher incidence at the higher dose, i.e., 300 mg QD. The changes in eGFR and electrolytes events regressed over time; although, in many cases did not return to patients' baseline levels over the duration of clinical trials (i.e., 26 or 52 weeks).

    - Conclusion:

      Given a modest increase in benefit with an increased risk of adverse events for 300 mg QD dose, compared to the 100 mg QD dose, this reviewer recommends a titration based dosing strategy. All patients can be initiated with the lower dose of 100 mg QD and escalated to the higher dose of 300 mg QD based on individual patient's tolerability, and need for further glycemic control.

- *Type 2 diabetes mellitus patients, who have moderate renal impairment (eGFR of 30-60 mL/min/1.73 m2):*
    - Benefit:

      Consistent with the known dependence of Canagliflozin mechanism of action on integrity of the renal function, we hypothesized there would be a

subset of patients with renal dysfunction that would exhibit diminished responses. Despite of dose-dependant decrease in HbA1c, both 100 mg QD and 300 mg QD doses showed only a modest efficacy in subjects with moderate renal impairment (Figure 2 DIA3004 results) when compared to type 2 diabetes mellitus subjects with normal renal function or mild renal impairment. The magnitude of response is markedly attenuated in the presence of moderate renal impairment. Further, both reduction in HbA1c (week 26 end-point) and eGFR from baseline (week 3 time-point) are dependent on dose and baseline eGFR in moderate RI patients (DIA3004).

The post-hoc evaluation of the data from Trial DIA3004, evaluating efficacy in subgroups using an eGFR cut-off of 40 mL/min/1.73m2, which was the median value of eGFR in this trial, demonstrated that the efficacy in patients with moderate renal impairment was primarily driven by the subjects with baseline eGFR≥40 mL/min/1.73m^2. In eGFR<40 mL/min/1.73m^2 group, reduction in HbA1c in patients receiving canagliflozin 100 mg or 300 mg did not appear to be different compared to placebo.

- Risk:

  There was a trend for dose–dependant decrease in eGFR in patients with moderate renal impairment following treatment with canagliflozin (as high as ~40 unit drop at individual level). This eGFR decline was also dependent on baseline renal function.

  The subjects with >30% reduction in eGFR from baseline at any time during the trial duration increased in dose dependent manner for both eGFR<40 and eGFR>=40 groups, albeit higher risk in the latter group. However, these eGFR changes appear to be transient although eGFR did not return to baseline in majority of subjects.

- Conclusion

  Given the lower response of canagliflozin in eGFR<40 mL/min/1.73m2 group and the increased risk of decline in renal function (eGFR) from baseline, the benefit-risk of canagliflozin is considered to be unfavorable in eGFR<40 mL/min/1.73m2 group. Although similar risks were present in eGFR>=40 mL/min/1.73m2 group, these patients benefit at both 100 and 300 mg canagliflozin doses compared to placebo. Therefore, benefit-risk of canagliflozin is considered to be favorable in eGFR>=40 mL/min/1.73m2 group when administered with caution.

  Therefore, this reviewer recommends that canagliflozin should be used only in eGFR≥40 mL/min/1.73m^2 group and not in patients with eGFR<40 mL/min/1.73m^2. These recommendations are based on the observations of no to minimal efficacy in eGFR <40 mL/min/1.73m^2 group, while still exposing these subjects to risk of decline in renal function, volume depletion adverse events and other unfavorable changes in laboratory markers.

- *Type 2 diabetes mellitus elderly patients and patients on loop diuretics:*

  The Sponsor's proposal of starting dose of 100 mg QD dose in elderly population and in patients on loop diuretics is reasonable based on safety and efficacy data and the canagliflozin could be used in alignment to the recommendations made above.

  In general, in patients treated with canagliflozin renal function and AEs related to volume depletion should be closely monitored during first 3-6 weeks and thereafter, periodically, if not frequently. This is more important if the dose is increased from 100 mg QD to 300 mg QD during therapeutic use. Phase 3 trials did not test this option and the volume depletion events occurred earlier when patients were treated with starting dose of 300 mg QD in Canagliflozin program.

1.2 Recommendations

Division of Pharmacometrics finds the NDA 204042 approvable from a clinical pharmacology perspective. Please refer to section 1.1 of the clinical pharmacology QBR for OCP recommendations.

1.3 Labeling Recommendations

Discussions on how to label the Dosing &Administration section are ongoing with the clinical review team but our specific recommendations on dosing are provided in section 1.1 of the Clinical Pharmacology QBR. The following are the labeling recommendations relevant to clinical pharmacology for NDA 204042 that were based on population PK analysis. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12.3 Pharmacokinetics

Effects of Age, Body weight, Gender and Race

Based on the population PK analysis with data collected from 1526 subjects, age, BMI, gender, and race do not have a clinically meaningful effect on pharmacokinetics of canagliflozin [see Dosage and Administration (2.3); Warnings and Precautions (5.2); Adverse Reactions (6.1); Special Populations (8.5)].

(b) (4)

[redacted]

(b) (4)

Reviewer's comments:

- *Proposed labeling claim by the Sponsor that "there is no clinically meaningful effect of age, BMI, gender, and race on canagliflozin pharmacokinetics" is acceptable. However,* (b) (4) *have been removed to keep the label concise.*
- *No labeling claim on the renal function is proposed based on the population pharmacokinetic analysis. In this population PK analysis subjects with normal renal function subjects or subject with mild to moderate renal function were included. However, labeling claims for renal function are based on the dedicated renal impairment study (DIA1003) and Phase 3 trial in patients with moderate renal impairment (DIA3004). Renal function measurement by estimated glomerular filtration rate (eGFR) was identified as a statistically significant covariate on the elimination rate of canagliflozin. However, systemic exposure - efficacy relationship was flat over a wide range of canagliflozin exposure in trial DIA3005. Efficacy in Phase 3 trials was slightly lower in subjects with mild renal impairment in comparison to that of subjects with normal renal function, however, the magnitude of reduction in HbA1c was still clinically relevant. Sponsor conducted a dedicated Phase 3 study in type 2 diabetic subjects with moderate renal impairment. Results of this Phase 3 trial showed efficacy of canagliflozin in terms of statistically significant lowering of HbA1c in comparison to the placebo, however, despite of comparable range of systemic exposure, the magnitude of reduction in HbA1c was remarkably lower in comparison to the type 2 diabetic subjects with normal renal function or mild renal impairment.*

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

The final population PK analysis for canagliflozin included pooled data from nine Phase 1 studies (i.e., DIA1001, DIA1002, DIA1003, DIA1007, DIA1008, DIA1019, DIA1023, DIA1030, and TA7284-02), two Phase 2 studies (i.e., DIA2001, OBE2001) and three Phase 3 studies (i.e., DIA3004, DIA3005, and DIA3009). Primary objective of the population PK analysis was to:

- Describe the PK of canagliflozin in healthy subjects and in patients with type 2 diabetes mellitus (T2DM) after oral administration
- Identify patient factors (age, race, gender, renal function, body weight etc.) that may affect PK and, therefore, require dose adjustment

2.1.1 Methods

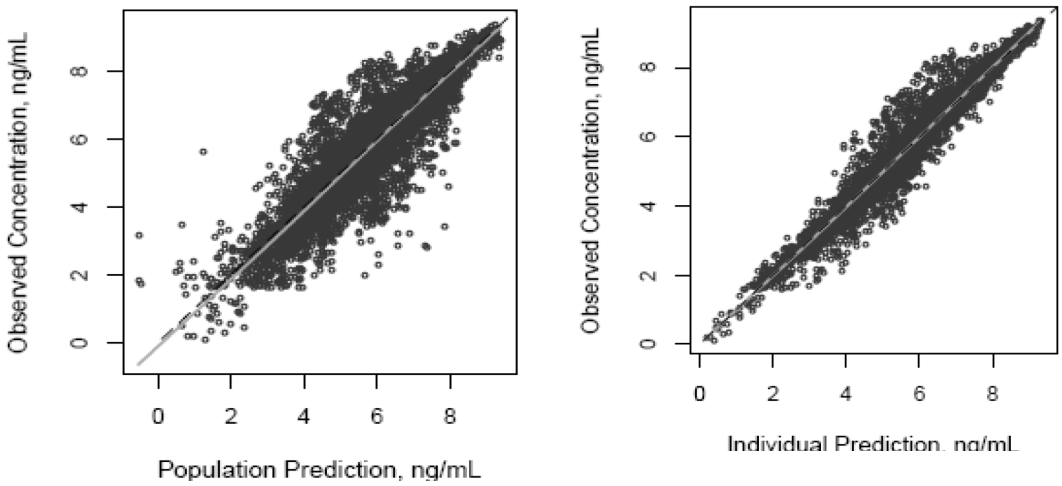
Total of 5,715 PK samples from 245 subjects across the nine richly sampled Phase 1 studies from dataset (cana-pk-nm-phase1-20120113-02.csv), which was used for model

and covariate model development on Phase 1, were included in the population PK analysis. Once the structural model and statistically significant covariates on absorption (ka and Tlag) and distribution (Vc/F) parameters, were identified, the dataset was combined with data from two sparsely sampled Phase 2 studies and three sparsely sampled Phase 3 studies. From this combined dataset (cana-pk-nm-int-3-tr-20120224-cl.csv), 8,813 PK samples from 1,526 subjects were included in the analysis. This combined dataset included only PK samples collected up to the primary endpoint (i.e. week 26 for DIA3004 and DIA3005 and week 52 for DIA3009).

Plasma canagliflozin concentration-time data were analyzed by non-linear mixed-effects modeling using NONMEM (ICON plc) Version VII level 1.0, with PREDPP version V level 2.0 with the gFortran compiler 4.5.0. The FOCE method with interaction was used for all analyses. The model was parameterized in terms of rate constants using the ADVAN4 TRANS3 option in NONMEM.

2.1.2 Final Model

A 2-compartment population PK model with sequential zero- and first order absorption and first order elimination, with IIV on Vc/F, ke, ka, k32 and Tlag was selected as the structural model to describe Canagliflozin PK. To arrive at the final model, the full model was subjected to a stepwise backward elimination procedure. In the final covariate model (run510, Table 6), the following six covariate-parameter combinations were identified on the absorption (ka and Tlag) and distribution (Vc/F) parameters: BMI on ka, BMI and over-encapsulation [over-encapsulated vs. non-encapsulated tablets] on Tlag and body weight, age and gender on Vc/F. The IIV parameters of the base model were specified by a lognormal distribution. The residual error (intra-individual variability) parameters of the final model were described by combined error model. Basic goodness of fit plots for the Sponsor's final model are shown in Figure 14.



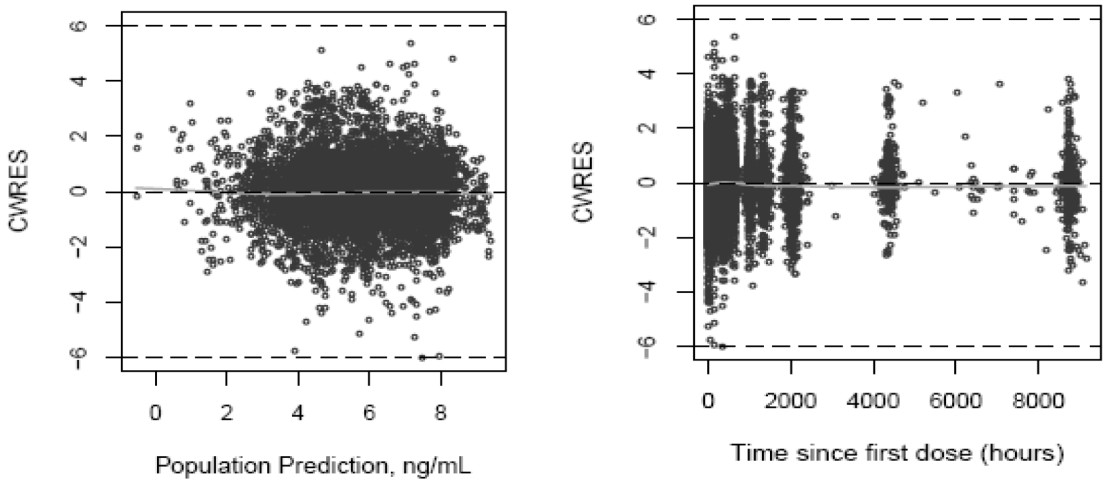


Figure 14: Basic goodness of fit plots for the Sponsor's final model (with Phase 1 and Phase 3 Data) with covariate effects of Weight, Age and Gender on *Vc/F*, BMI on *ka*, BMI and Over- encapsulation on *Tlag* and eGFR and Dose on *ke*

Source: Population PK Study Report, Page 43

The parameter estimates for the final phase 1 and phase 3 data presented in Tables 5 and 6, respectively.

Table 5: Parameter Estimates of Final Model (Using Phase 1 Data)

Parameter		Population Mean Estimate	Relative Standard Error (RSE%)	Inter-Individual Variability (%CV)
V_c/F	(L) (males)	99.3	2.0	15
k_e	(hr^{-1})	0.150	2.1	20
k_a	(hr^{-1})	3.68	13.7	123
T_{lag}	(hr) (non-encaps. tablet)	0.147	9.0	79
D_1	(hr)	0.604	8.9	
k_{23}	(hr^{-1})	0.101	4.8	
k_{32}	(hr^{-1})	0.0856	3.9	35
V_c/F	(L) (females)	82.6	2.7	
T_{lag}	(hr) (over-encaps. tablet)	0.262	14.0	
Body Weight on V_c/F		0.583	8.5	
Age on V_c/F		-0.167	21.3	
Body mass index on k_a and T_{lag}		1.41	21.6	
Residual variability (%)		22.9	9.7	

V_c/F = apparent volume of distribution of central compartment
k_a = absorption rate constant
k_e = elimination rate constant
T_{lag} = lag-time
D_1 = duration of zero-order input into gut compartment
k_{23}, k_{32} = distribution rate constants to and from peripheral compartment

Source: Population PK Study Report, Pages 101

Table 6: Parameter Estimates of Final Model (After incorporating Phase 3 data)

Parameter		Population Mean Estimate	Relative Standard Error (RSE%)	Inter-Individual Variability (%CV)
V_c/F	(L) (males)	99.3 FIX		15 FIX
k_e	(hr^{-1})	0.145	1.0	23
k_a	(hr^{-1})	3.68 FIX		123 FIX
T_{lag}	(hr) (non-encaps. tablets)	0.147 FIX		79 FIX
D_1	(hr)	0.604 FIX		
k_{23}	(hr^{-1})	0.101 FIX		
k_{32}	(hr^{-1})	0.0856 FIX		35 FIX
V_c/F	(L) (females)	82.6 FIX		
T_{lag}	(hr) (over-encaps. tablets)	0.262 FIX		
Body weight on V_c/F		0.583 FIX		
Age on V_c/F		-0.167 FIX		
Body mass index on k_a and T_{lag}		1.41 FIX		
eGFR on k_e		0.261	9.0	
Dose on k_e		-0.0631	16.2	
Residual variability (%) Phase 1		20.2	4.9	
Residual variability (%) Phase 2 and 3		55.9	6.0	

V_c/F = apparent volume of distribution of central compartment
k_a = absorption rate constant
k_e = elimination rate constant
T_{lag} = lag-time
D_1 = duration of zero-order input into gut compartment
k_{23}, k_{32} = distribution rate constants to and from peripheral compartment
eGFR = estimated glomerular filtration rate
CL/F = apparent total clearance
FIX = absorption (k_a, T_{lag} and D_1) and distribution (V_c/F, k_{23} and, k_{32}) parameters, including covariate and random effects, were fixed to the values obtained from the model built on Phase 1 data

Source: Sponsors Population PK Report, Pages 101

For a typical non-diabetic subject (i.e. age = 45 yr; body weight = 75.8 kg; BMI = 26.1 kg/m^2), the apparent canagliflozin clearance was estimated at 14.9 L/hr (males) and 12.4 L/hr (females) with an IIV (on ke) of 20% and was in accordance with non-compartmental estimates (14.8 L/hr, CSR DIA1003). The apparent volume of distribution was estimated to be approximately 99.3 L in males and 82.6 L in females with an IIV of 15%. The IIV on the distribution rate constant from the peripheral to the central compartment (k32) was moderate (35%). The population parameters describing absorption comprised a Tlag of 0.147 hr, a D1 of 0.604 hr, and a ka of 3.68 hr^{-1}. The estimated IIV for ka and Tlag was high, i.e. 123% and 79% CV, respectively.

Figure 15 and 16 show separate visual predictive check (VPC) subplots of the final model (Run549) of all 100 and 300 mg data, respectively, from the three Phase 3 studies (DIA3004, DIA3005 and DIA3009). In these plots, the medians of the simulated individual concentration-time profiles and the area bounded by the 90% prediction interval around them are plotted over the observed concentrations. Overall, approximately 90% of the observations lie within the predicted interval, indicating that model adequately describes the data.

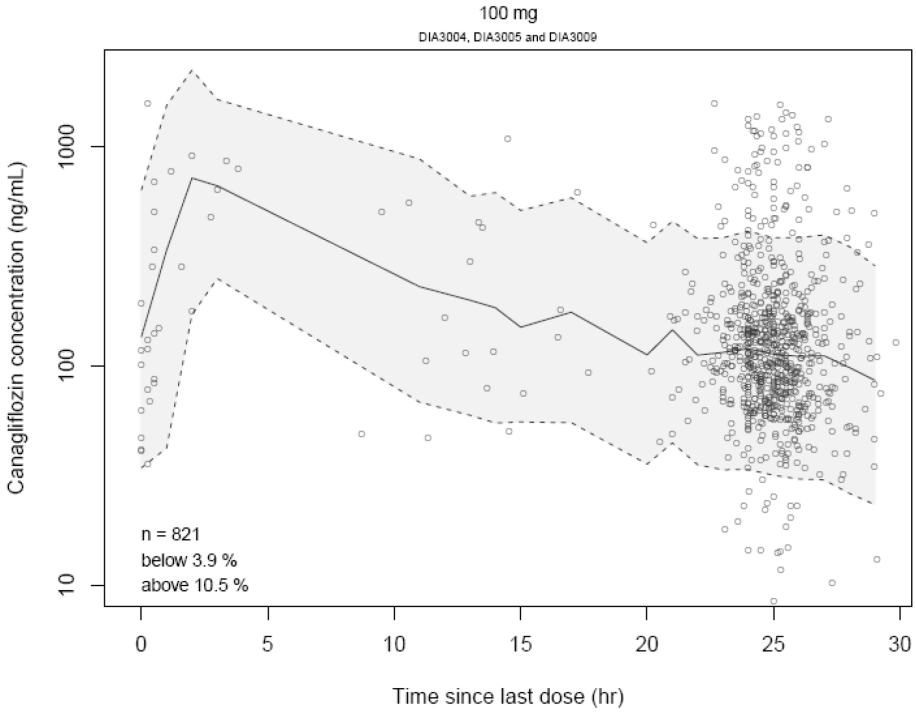


Figure 15: Visual Predictive Check of 100 mg Data From Phase 3 using final model
Source: Sponsors Population PK Report, Pages 47-48
200 databases were simulated using the study design and covariate distributions of the study population. **grey solid line:** median of simulations; **grey dotted lines:** percentiles of 90% prediction interval; **grey symbols:** observed canagliflozin concentrations.

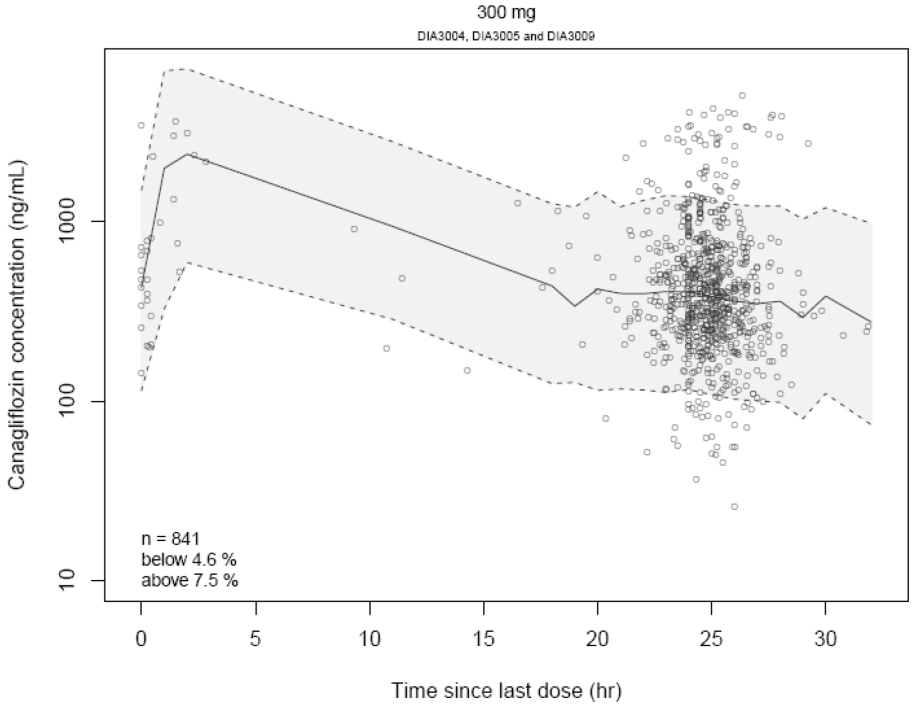
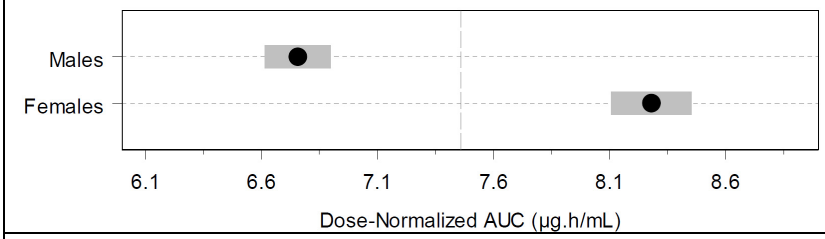
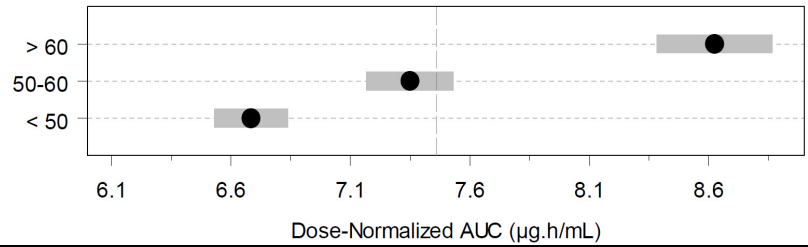
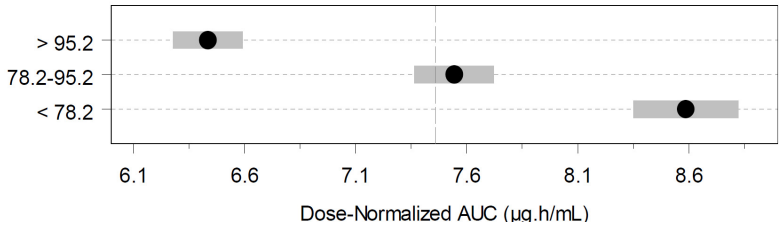
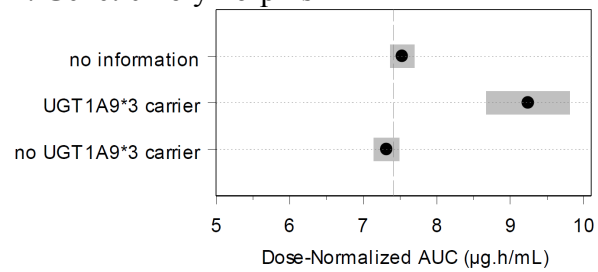
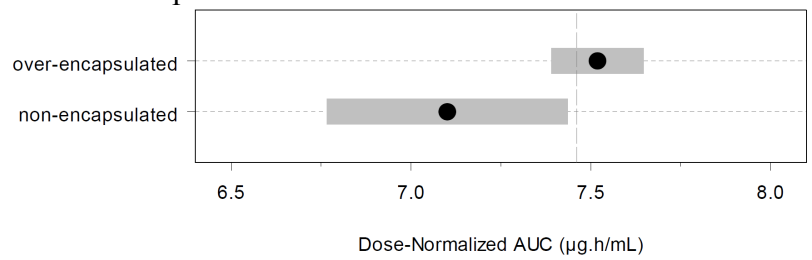


Figure 16: Visual Predictive Check of 300 mg Data From Phase 3 using final model
Source: Sponsors Population PK Report, Pages 47-48
200 databases were simulated using the study design and covariate distributions of the study population. **grey solid line:** median of simulations; **grey dotted lines:** percentiles of 90% prediction interval; **grey symbols:** observed canagliflozin concentrations.

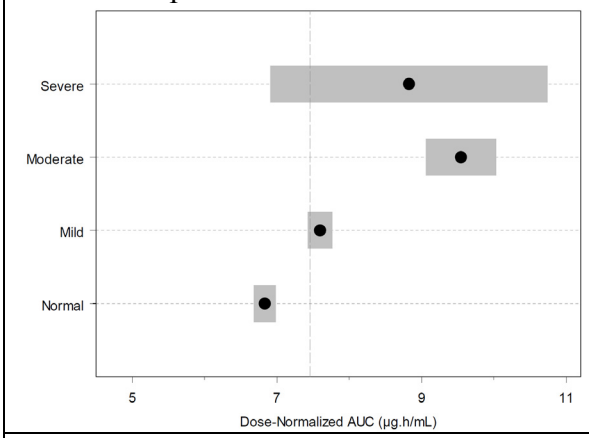
2.1.2.1 Canagliflozin Covariate Effects

The covariates included in the final model were BMI on *ka*, BMI and over-encapsulation [overencapsulated vs. non-encapsulated tablets] on *Tlag*, gender, age and body weight on *Vc/F*, and eGFR and dose on *ke*. eGFR, dose and genetic polymorphism (carriers of the UGT1A9*3 allele) were identified as statistically significant covariates on *ke*. The covariate effect of eGFR on *ke,* and hence clearance, indicates that *CL/F* of canagliflozin is dependent on renal function.

For example, subjects with body weight <78.2 kg will have about 33% higher median dose-normalized AUC values than subjects with a body weight >95.2 kg. Results from this analysis indicate that subjects older than 60 years have higher median dose-normalized AUC values, by 29%, when compared to younger adults (<50 years) due to the reduced apparent volume of distribution in elderly. Similarly, only a minor increase (~22%) in dose-normalized AUC was observed in females compared to male subjects and is attributed to the lower apparent volume of distribution in females. The median dose-normalized AUC values were about 11%, 40%, and 29% higher in subjects with mild (60-89 mL/min/1.73 m2), moderate (30-59 mL/min/1.73 m2), and severe (15-29 mL/min/1.73 m2) RI, respectively, as compared to the normal renal function group (≥ 90 mL/min/1.73 m2). From this population PK analysis, subjects (n=21) carrying the UGT1A9*3 allele had somewhat higher (about 26%) exposure (median dose-normalized AUC values) than subjects not carrying the UGT1A9*3 allele (n=700).

A. Gender  	Males n=769 Females n=847 n= number of subjects.
B. Age  	Age < 50 yr n=533 50 ≤ Age ≤ 60 yr n=602 Age > 60 yr n=481 n= number of subjects.
C. Body Weight  	WT < 78.2 kg n=536 78.2 ≤ WT ≤ 95.2 kg n=543 WT > 95.2 n=537 n= number of subjects.
D. Genetic Polymorphism  	No information on the UGT1A9 genotype: n=895 UGT1A9*3 carriers: n=21 No UGT1A9*3 carriers: n=700 n= number of subjects.
E. Over-encapsulation  	over-encapsulated tablet n=1442 non-encapsulated tablet n=174 n= number of subjects.

F. Renal Impairment



Normal renal function: ≥ 90 mL/min/1.73 m^2 : n=718
Mild renal impairment: 60-89 mL/min/1.73 m^2 : n=663
Moderate renal impairment: 30-59 mL/min/1.73 m^2 : n=209
Severe renal impairment: 15-29 mL/min/1.73 m^2 : n=18
n= number of subjects.

Grey Bars: 95% CI; **Filled Circle**: Median; **Vertical Line**: Median Population Dose-Normalized AUC.

Figure 17: Summary of Predicted Dose-normalized Steady State Canagliflozin Exposures in Subjects with T2DM
Source: Sponsors Population PK Report, Pages 50, 51, and 56

These data are generally consistent with the observed Phase 1 data. For example, in the renal impairment study DIA1003 (CSR DIA1003 2011), the geometric least squares mean AUCinf values were approximately 15%, 29%, and 53% higher in subjects with mild, moderate, and severe renal impairment, respectively.

2.2 Sponsor's Conclusions

- A 2-compartment population PK model for canagliflozin with sequential zero- and first order absorption and first order elimination, with IIV on Vc/F, ke, ka, k32 and Tlag best fits the data.
- Gender, age and body weight on Vc/F, BMI on ka and BMI and over-encapsulation [overencapsulated vs. non-encapsulated tablets] on Tlag were identified as the most significant covariates affecting the absorption and distribution characteristics of canagliflozin in this population PK analysis. These effects are not of significant magnitude to be deemed clinically relevant and therefore no dosage adjustment is necessary based on gender, age, or body weight.
- eGFR, dose and genetic polymorphism (carriers of the UGT1A9*3 allele) were identified as statistically significant covariates affecting ke and thus CL/F of canagliflozin. Given the small effect size of these covariates on the PK (AUC) of canagliflozin, they are not deemed to be of clinical relevance and therefore no dosage adjustment is required based on eGFR or genotype.
- No statistically significant effects of age, gender, race, glycemic status, fed status, chronic concomitant medications [substrates of UGT1A9 or UGT2B4], and PSD on ke and hence CL/F of canagliflozin could be observed.
- In summary, although the effects of gender, age, and body weight on Vc/F and eGFR, dose and genetic polymorphism on ke were statistically significant, given

the small magnitude of these effects, they are considered not to be of clinical relevance, and no dose adjustment is warranted.

***Reviewer's comments on Sponsor's Population PK Analysis**:*

- *Sponsor's population PK analysis is generally adequate. However, parameterization in form of CL and V would have been more relevant physiologically, and easy to relate biologically to the covariates.*
- *Nevertheless, the covariates that were identified in the final model are likely not to be clinically significant as the magnitude of effect on systemic exposure of Canagliflozin is within 20-30%.*
- *No labeling claim on the renal function is proposed based on the population pharmacokinetics analysis. Renal function measurement by calculated creatinine clearance, cCrCL, was identified as a statistically significant covariate on the apparent clearance of canagliflozin. In this population PK analysis subjects with normal renal function, with mild or moderate renal impairment were included. Efficacy in Phase 3 trials were slightly lower in patients with mild renal function and that of subjects with normal renal function. Sponsor conducted a dedicated Phase 3 study in patients with moderate renal function. Results of this Phase 3 trial showed modest efficacy of canagliflozin in terms of lowering of HbA1c although it was statistically significant different from the placebo.*
- *Sponsor's conclusion that no dose adjustment based on age, gender, body mass index, and race is supported by the population PK analysis results and is acceptable. See reviewer's independent analysis in section 3.3.*

3 RESULTS OF REVIEWER'S ANALYSIS

3.1 Objectives

The primary objective was to confirm the proposed label claims that there are no clinically meaningful effects of gender, BMI, age, race on Canagliflozin pharmacokinetics.

3.2 Methods

3.2.1 Data Sets

Data sets used are summarized in Table 7.

Table 7: Analysis Data Set

Name	Link to EDR
cana-pk-nm-phase1-20120113-csv.xpt (For Phase 1 base model run147) cana-pk-nm-phase1-20120113-02-csv.xpt (For Phase 1 full model run510) cana-pk-nm-3-tr-20120224-cl-csv.xpt ((For Phase 1 full model run549) cana-pk-nm-3-tr-20120321-cl-csv.xpt(For Phase 1 full model run549)	\\Cdsesub1\evsprod\NDA204042\0000\m5\datasets\pop-pk\ analysis\ legacy\ datasets

3.2.2 Software

NONMEM version 7.2 and R V2.11.0 were used for reviewer's analysis.

3.3 Results

The apparent clearance showed a decreasing trend with increase in age, (Figure 18). However, since eGFR and age are negatively correlated in the MDRD equation, the eGFR can provide the physiological explanation of decrease in CL with age.

A. CL vs. AGE **B. CL vs. eGFR**

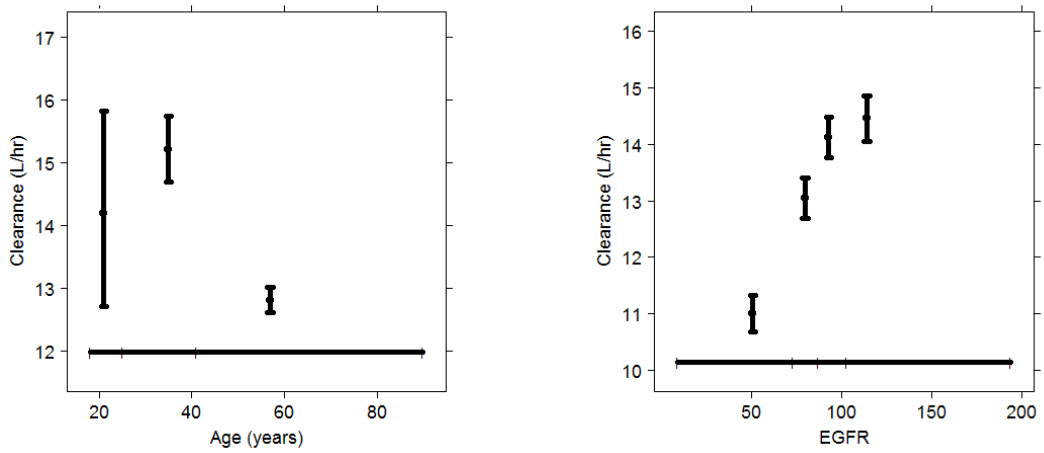
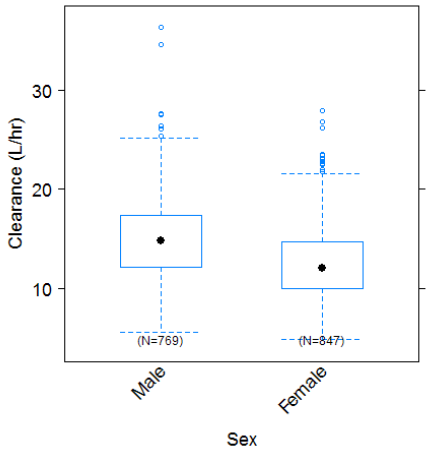


Figure 18: Relationship between individual post-hoc estimates of cangliflozin apparent clearance (CL/F) with covariates identified during the model development was consistent in the final model run (run 549) with Phase 3 data

There was no effect of race on canagliflozin clearance, while females showed lower clearance than males (Figure 19). CL was impacted by body weight (and thus BMI being a derived covariate). Since sponsor used ke*Vd/F for computing CL in their model and weight was a covariate on V, the observed CL and weight relationship is reasonable to expect.

A. Boxplot of CL vs. GENDER



B. Boxplot of CL vs. Race

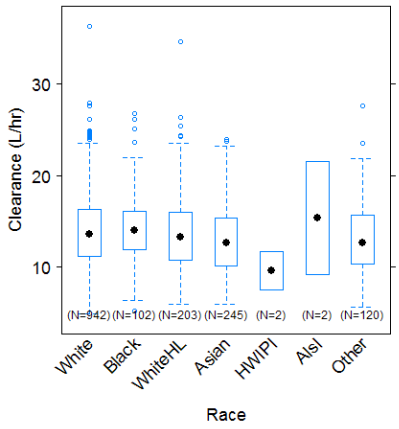
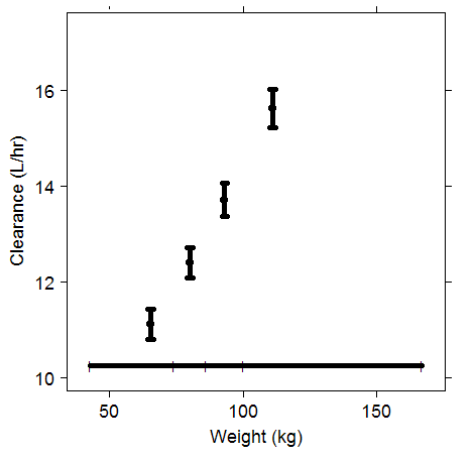


Figure 19: Relationship between individual post-hoc estimates of cangliflozin apparent clearance (CL/F) with covariates identified during the model development was consistent in the final model run (run 549) with Phase 3 data

A. CL vs. Body Weight



B. CL vs. BMI

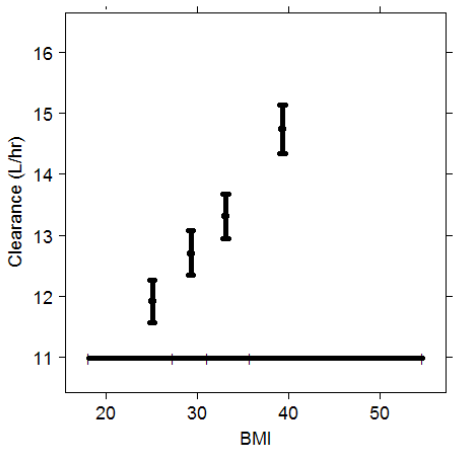


Figure 20: Relationship between individual post-hoc estimates of cangliflozin apparent clearance (CL/F) with covariates identified during the model development was consistent in the final model run (run 549) with Phase 3 data

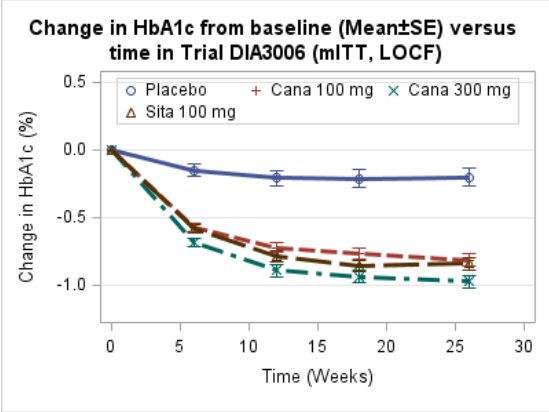
Using the sponsor's base model and final model, the parameter-covariate relationship was consistent with the claims (Appendix 4.3 Figure 25). The parameter-covariate relationships were consistent with the covariates retained in the final model (Appendix 4.2 Figures 22 and 24).

4 APPENDIX TO PHARMACOMETRIC REVIEW

Appendix 4.1: Longitudinal Efficacy Data from Add-on Therapy Trials

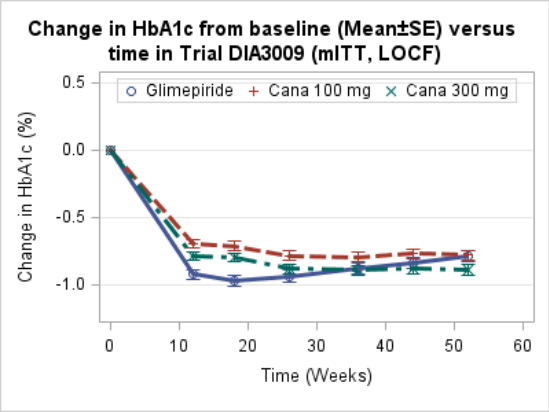
The time-profiles for the mean change from baseline in HbA1c in add-on therapy trials are shown in Figure 21 below.

A. Add on to metformin

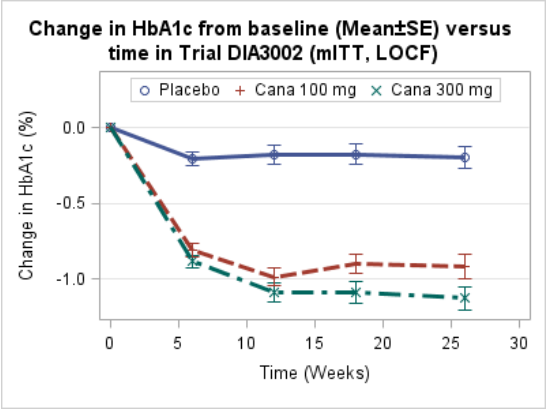


Sita- Sitagliptin, DPP4 inhibitor

B. Add on to metformin (no placebo)



C. Add on to metformin and sulfonylurea



D. Add on to metformin and pioglitazone

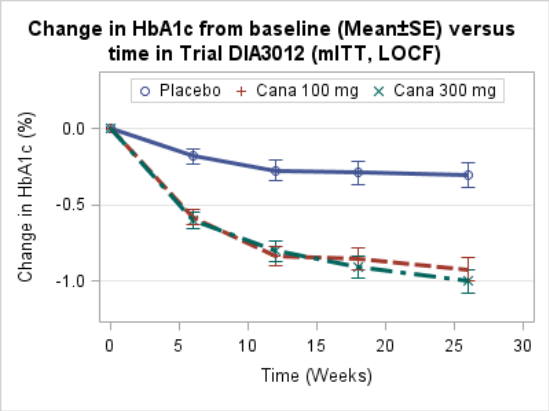
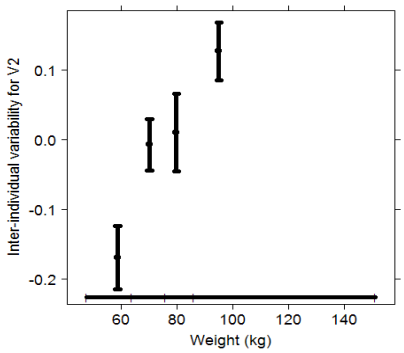


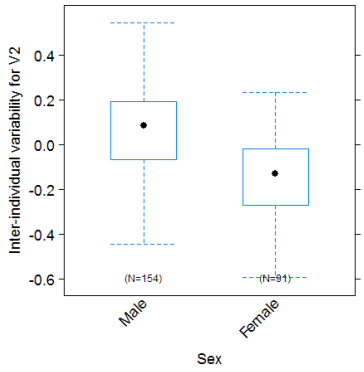
Figure 21: Time-profiles for mean (±SE) change from baseline in HbA1c in Phase 3 trials.

Appendix 4.2: Parameter-COVARIATE Relationship from Sponsor's Model

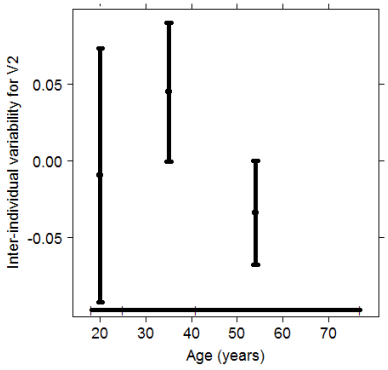
A. IIV on V2 vs. Weight



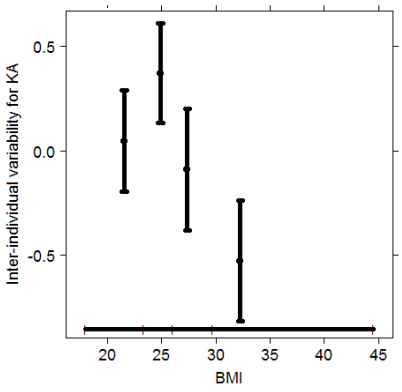
B. Box-plots of IIV on V2 vs. SEX



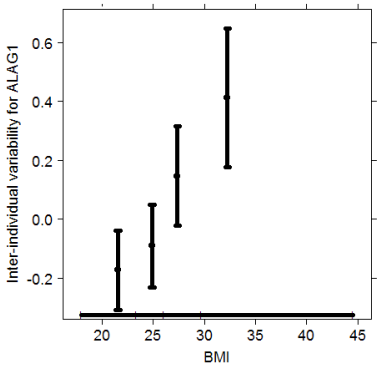
C. IIV on V2 vs. Age



D. IIV on Ka vs. BMI



E. IIV on Tlag vs. BMI



F. IIV on Tlag vs. Form (Non-encapsulated=0 over-encapsulated =1)

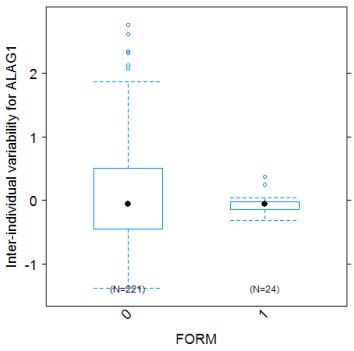
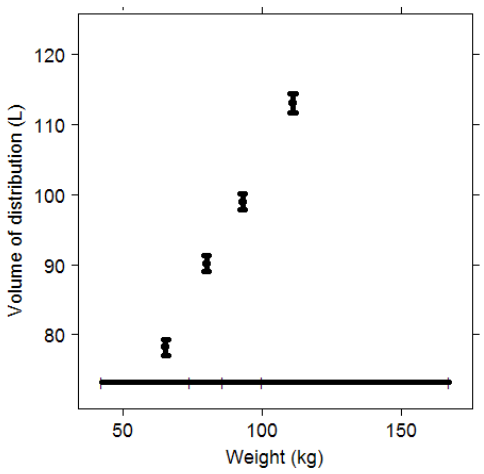
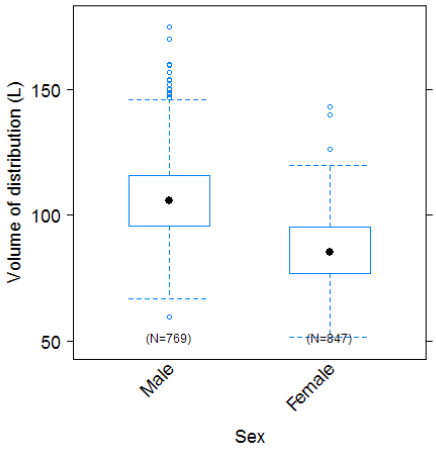


Figure 22: Confirmation of inter-individual variability (IIV) on Canagliflozin PK parameters (V2, Ka, and ALAG1 (Tlag)) versus covariates from base model

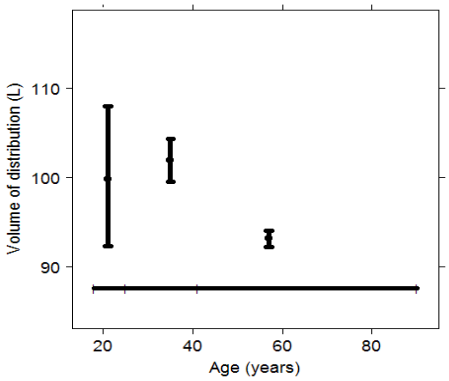
A. V2 vs. Weight



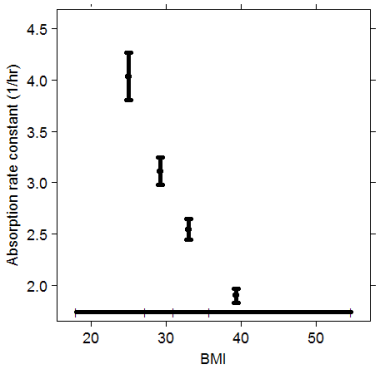
B. Boxplot of V2 vs. SEX



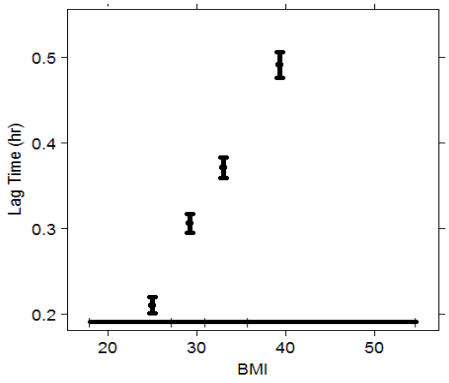
C. V2 vs. Age



D. Ka vs. BMI



E. Tlag vs. BMI



F. Ke vs. eGFR

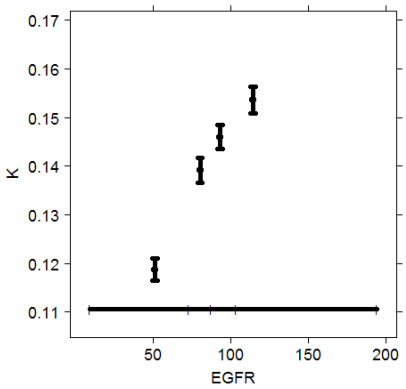
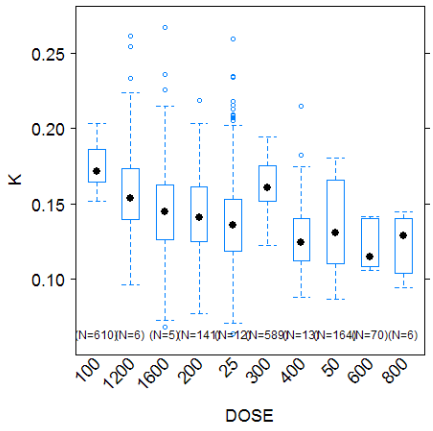
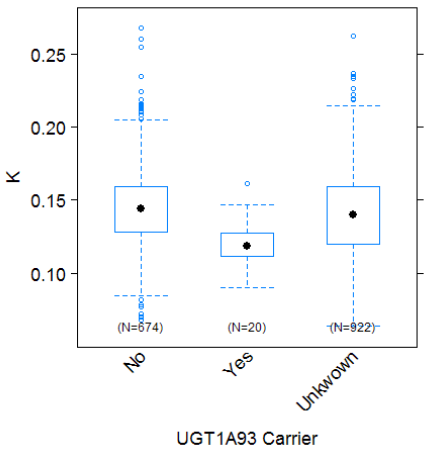


Figure 23: Relationship of parameters with covariates identified during the model development was consistent in the final model run (run 549) with Phase 3 data

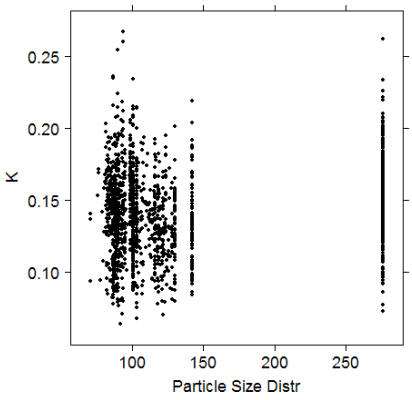
A. Ke vs. Dose



B. Boxplot of Ke vs. PGx



C. Ke vs. PSD (particle-size distribution)



D. Ke vs. Race

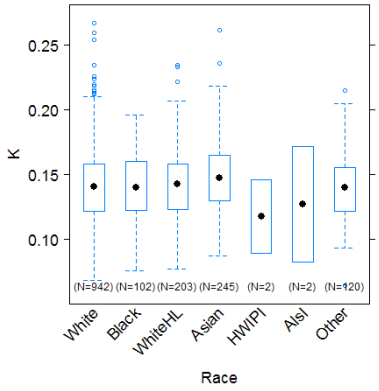


Figure 24: Relationship of parameters with covariates identified during the model development was consistent in the final model run (run 549) with Phase 3 data

The parameter-covariate relationships were consistent with the covariates retained in the final model (Figures 24, 25 and 26).

Appendix 4.2: Additional Supportive Tables and Graphs

Table 8: Number of Subjects with Volume Depletion Adverse Events by Selected Baseline Characteristics - Regardless of Use of Rescue Medication (ISS Phase 3 Broad Dataset: Safety Analysis Set)

	% (n) in population[b]	Incidence[a]			
		Cana 100 mg % (n/N)	Cana 300 mg % (n/N)	All Cana % (n/N)	All Non-Cana % (n/N)
eGFR (mL/min/1.73m^2)	N = 9432				
<60	13.0% (n=1223)	4.7% (18/382)	8.1% (33/405)	6.5% (51/787)	2.5% (11/436)
60 to <90	54.6% (n=5154)	2.4% (40/1686)	2.9% (48/1680)	2.6% (88/3366)	1.5% (26/1788)
≥90	32.4% (n=3055)	1.3% (13/1021)	2.4% (24/999)	1.8% (37/2020)	1.2% (12/1035)
Sex	N = 9439				
Male	58.2% (n=5493)	2.6% (46/1803)	4.3% (76/1766)	3.4% (122/3569)	1.6% (31/1924)
Female	41.8% (n=3946)	1.9% (25/1289)	2.2% (29/1319)	2.1% (54/2608)	1.3% (18/1338)
Age (years)	N = 9439				
<65	69.0% (n=6509)	1.5% (31/2110)	2.7% (58/2114)	2.1% (89/4224)	1.4% (31/2285)
≥65	31.0% (n=2930)	4.1% (40/982)	4.8% (47/971)	4.5% (87/1953)	1.8% (18/977)
Age (years)	N=9439				
<75	94.8%(n= 8949)	2.2% (63/2929)	3.1% (90/2913)	2.6%(153/5842)	1.4% (45/3107)
≥75	51.9% (n=490)	4.9% (8/163)	8.7% (15/172)	6.9% (23/335)	2.6% (4/155)
Baseline HbA1c (%)	N = 9434				
≤7.9	51.9% (n=4894)	2.4% (37/1563)	2.9% (47/1607)	2.6% (84/3170)	1.6% (27/1724)
>7.9	48.1% (n=4540)	2.2% (34/1527)	3.9% (58/1477)	3.1% (92/3004)	1.4% (22/1536)
Use of ACE/ARB	N = 9439				
No	31.4% (n=2961)	1.2% (12/970)	1.5% (15/969)	1.4% (27/1939)	1.0% (10/1022)
Yes	68.6% (n=6478)	2.8% (59/2122)	4.3% (90/2116)	3.5% (149/4238)	1.7% (39/2240)
Use of Diuretics[c]	N = 9439				
No	64.8% (n=6118)	2.1% (42/2016)	2.3% (47/2009)	2.2% (89/4025)	1.1% (24/2093)
Yes	35.2% (n=3321)	2.7% (29/1076)	5.4% (58/1076)	4.0% (87/2152)	2.1% (25/1169)
Use of Loop Diuretics	N = 9439				
No	92.4% (n=8717)	2.2% (64/2876)	2.9% (83/2835)	2.6% (147/5711)	1.2% (37/3006)
Yes	7.6% (n=722)	3.2% (7/216)	8.8% (22/250)	6.2% (29/466)	4.7% (12/256)
Use of ACE/ARB and/or Diuretics	N = 9439				
None	27.7% (n=2611)	1.1% (10/871)	1.3% (11/850)	1.2% (21/1721)	0.9% (8/890)
ACE/ARB only	37.2% (n=3507)	2.8% (32/1145)	3.1% (36/1159)	3.0% (68/2304)	1.3% (16/1203)
Diuretics only	3.7% (n=350)	2.0% (2/99)	3.4% (4/119)	2.8% (6/218)	1.5% (2/132)
ACE/ARB and diuretics	31.5% (n=2971)	2.8% (27/977)	5.6% (54/957)	4.2% (81/1934)	2.2% (23/1037)
Duration of Diabetes (years)	N = 9439				
<10	49.8% (n=4705)	1.8% (27/1536)	1.9% (29/1502)	1.8% (56/3038)	1.1% (18/1667)
≥10	50.2% (n=4734)	2.8% (44/1556)	4.8% (76/1583)	3.8% (120/3139)	1.9% (31/1595)
Diabetes Complications	N = 9439				
No	66.9% (n=6312)	1.5% (32/2066)	2.4% (48/2032)	2.0% (80/4098)	1.4% (31/2214)
Yes	33.1% (n=3127)	3.8% (39/1026)	5.4% (57/1053)	4.6% (96/2079)	1.7% (18/1048)
Systolic Blood Pressure (mmHg)	N = 9439				
≤110	6.1% (n=575)	4.5% (8/178)	6.0% (11/184)	5.2% (19/362)	2.3% (5/213)
>110	93.9% (n=8864)	2.2% (63/2914)	3.2% (94/2901)	2.7% (157/5815)	1.4% (44/3049)

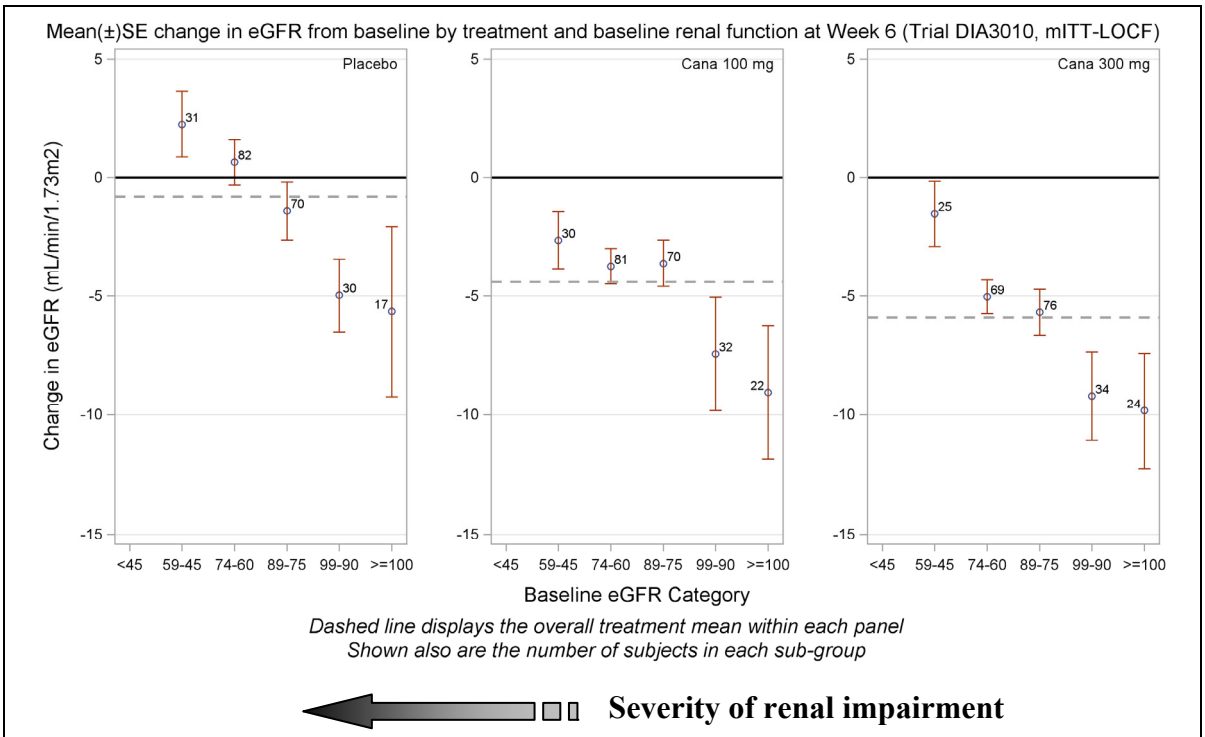


Figure 25: Change in eGFR from baseline by treatment and baseline renal function (eGFR) in elderly population [DIA3010; mITT, Week 6]. Note there were no subjects in <45 eGFR group.

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

/s/

JAYABHARATHI VAIDYANATHAN
02/06/2013

MANOJ KHURANA
02/06/2013

LYLE CANIDA
02/06/2013

NITIN MEHROTRA
02/06/2013
Anshu Marathe was the secondary PM reviewer

MICHAEL A PACANOWSKI
02/06/2013

LOKESH JAIN
02/06/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	204-042	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Date:	May 31, 2012		
Division:	DMEP	**Acting Biopharmaceutics Team Leader:** John Z. Duan, Ph.D.	
Applicant:	Janssen Research and Development, LLC.		
Trade Name:	Invokana®	**Date Assigned:**	June 6, 2012
Generic Name:	Canagliflozin (JNJ-28431754)	**Date of Review:**	January 28, 2013
Indication:	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	**Type of Submission:** Original New Drug Application	
Formulation/strengths	Film-coated tablet/100 mg and 300 mg		
Route of Administration	Oral		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

SUBMISSION:

Canagliflozin is an inhibitor of sodium-glucose transporter 2 (SGLT2). The inhibition of SGLT2 is expected to decrease renal glucose re-absorption and increase urinary glucose excretion, resulting in lower plasma glucose in patients with type 2 diabetes. The drug product is a film-coated oral tablet formulated for immediate release in two strengths, 100 mg and 300 mg. The recommended dose of canagliflozin is 100 mg or 300 mg once daily. The proposed commercial formulation is a debossed tablet (b) (4), and film-coated in yellow (100-mg) or white (300-mg).

The Applicant (b) (4) To bridge drug product manufactured with (b) (4) drug substance and drug product manufactured with (b) (4) drug substance, the Applicant performed several non-direct BE assessments including physicochemical characteristics evaluation, GastroPlus Simulations, cross-study comparisons of PK data, population pK analysis, and a non-clinical bioavailability study in dogs. OCP and PharmTox reviewed these studies.

(b) (4) and used in all Phase 3 studies. The Applicant performed non-direct BE assessments to study the effect of over-encapsulation on the bioavailability of canagliflozin including cross-study comparisons of clinical PK data and population PK analysis, which are reviewed by OCP.

The dissolution profiles comparing tablets manufactured with (b) (4) drug substance and (b) (4) drug substance, and comparing over-encapsulated and non-encapsulated tablets were generated by a method, which was not the proposed regulatory dissolution method. The results are not reliable. Therefore, it is critical to evaluate the clinical cross-study comparisons of PK data and population PK analysis. According to the assessment of the Clinical Pharmacology reviewer, Dr. Jayabharathi Vaidyanathan, there is no concern of the effects of drug substance (b) (4) on bioavailability of canagliflozin manufactured using (b) (4) API lots, as the API lots from both were used in all the trials (Phase 1, 2 and 3), and the (b) (4) of the (b) (4) API lots used in Phase 3 were similar. Additionally, the population PK analysis did not find a significant difference when using either the (b) (4) APIs. Also, per Dr. Vaidyanathan, the over-encapsulation had a slight effect on absorption (affecting lag time) and exposure (a slight increase in AUC) but, these effects were not clinically relevant. Furthermore, Over-

encapsulated tablets were used in many Phase 1 trials, including BA, some DDI, and QT studies. The PK parameters in these trials were comparable to those in the trials using non-encapsulated tablets. Therefore, we can conclude: 1) the products manufactured with (b) (4) drug substance and (b) (4) drug substance can be considered similar; 2) the encapsulated and non-encapsulated tablets can be considered similar.

Both strengths are (b) (4). Therefore, it is acceptable to waive the requirement for an in-vivo study to characterize the bioavailability of the100 mg tablet strength based on dissolution profile similarity.

Initially, (b) (4) To bridge between the (b) (4) tablet (b) (4) and (b) (4) tablet (b) (4) the Applicant performed a relative bioavailability study (Study DIA1017) with single-dose administration of 300 mg Canagliflozin as (b) (4) tablets versus (b) (4) tablets (both manufactured using (b) (4)). Also, the Applicant performed food-effect study (Study DIA1043) to assess the bioavailability of 300 mg of Canagliflozin administered as the to-be-marketed tablet formulation ((b) (4) API). Both of these studies are reviewed by OCP.

The Applicant conducted the initial dissolution method (development dissolution method) using (b) (4) tablet which was thought to be the preferred dose at the time of method development. (b) (4) All clinical batches released met the dissolution acceptance criterion in place at the time of testing (Q= (b) (4)). However, the dissolution profiles obtained with the development method were fast for the 100 mg and 300 mg tablets. To obtain a more discriminating dissolution profile, (b) (4) The final dissolution method developed for canagliflozin 100 mg and 300 mg tablets employs a paddle apparatus with a concentration of 0.75% SLS in 600 mL water, and a rotation speed of 75 rpm. The designated registration stability batches were retested at the initiation of the stability study according to the proposed regulatory method (600 mL of 0.75% SLS in water as the dissolution medium). The proposed dissolution method for canagliflozin 100 mg and 300 mg tablets is acceptable. However, the proposed acceptance criterion is not acceptable as the registration, clinical and stability batches release > (b) (4) at 20 minutes. The Applicant is requested to change the acceptance criteria from Q= (b) (4) to Q= (b) (4) in 20 minutes.

It was noted that the commercial product is debossed while the clinical formulation is non-debossed. The Applicant did not submit comparative dissolution profiles to link the two formulations. Therefore, the Applicant is asked to submit dissolution profile comparisons between the debossed and non-debossed tablets.

Process development activities consisted of a DoE study conducted at the clinical manufacturing facility in (b) (4) at the (b) (4). The process DoE was conducted to evaluate the robustness of the formulation with regard to variation of (b) (4) This study was followed by process characterization studies at the proposed commercial manufacturing facility to define the proven acceptable ranges for the process parameters using the proposed commercial equipment and scale. (b) (4)

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 204-042 for canagliflozin film-coated tablet (100 mg and 300 mg) and has the following comments which should be conveyed to the Applicant:

1. Your proposed dissolution method is acceptable. However, your proposed acceptance criterion need to be revised to Q (b) (4) in 20 minutes. This requested revision is based on the performance of all clinical and stability batches and on the discriminating power of the method which indicated higher discriminating capability at earlier time points.

2. Submit dissolution profile comparisons between the to-be-marketed tablets (debossed) and the tablets used in clinical studies (non-debossed).

From the Biopharmaceutics perspective, a COMPLETE RESPONSE (CR) is recommended at this time for NDA 204-042 for canagliflozin tablets. This recommendation is due to an inconclusive agreement with the Applicant in terms of setting the dissolution acceptance criteria for canagliflozin Tablets. Once an agreement is reached, which is expected to occur the week of February 4th, a review addendum will be filed.

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

John Z. Duan, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: *NDA 204-042 DARRTS, RLostritto; ADorantes*

BIOPHARMACEUTICS ASSESSMENT

BIOPHARMACEUTIC INFORMATION:

Drug Substance

Canagliflozin is a [redacted] (b) (4) The solubility of the drug substance in aqueous media as a function of pH is shown in Table 1.

Table 1. Equilibrium Solubility of the Drug Substance in Aqueous Media as a Function of pH

Solvent	Solubility in Solution (g/100 mL)	Final pH
[redacted] (b) (4)		

The Applicant proposed acceptance criteria for the drug substance particle size as follows [redacted] (b) (4) The particle size acceptance criteria are based on the highest and lowest particle size of all [redacted] (b) (4) batches used in the production of the drug product.

Drug Product

The dosage form is a film-coated tablet formulated for immediate release in two strengths, 100 mg and 300 mg. The components and composition are shown in Table 2 for the 100 mg and in Table 3 for the 300 mg dosage strength.

Table 2: Components and Composition for the 100 mg Dosage Strength

Component	Quality Reference[a]	Role	% w/w	mg/unit
Core Tablet				
[redacted]				
Canagliflozin	Company standard	Active	[redacted]	[redacted]
Microcrystalline Cellulose	NF/Ph. Eur.			
Lactose Anhydrous	NF/Ph. Eur.			
Croscarmellose Sodium	NF/Ph. Eur.			
Hydroxypropyl Cellulose	NF/Ph. Eur.			
[redacted]	USP/Ph. Eur.			
[redacted]				
Magnesium Stearate[d]	NF/Ph. Eur.			[redacted]
Filmcoating				
[redacted] Yellow	Company standard			[redacted]
[redacted]	USP/Ph. Eur.			
		Total Tablet Weight		208.00

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.

[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous).

[redacted]

[d] Vegetable sourced

Table 3: Components and Composition for the 300 mg Dosage Strength

Component	Quality Reference[a]	Role	Theoretical % w/w	Theoretical mg/unit
Core Tablet (b) (4)				
Canagliflozin	Company standard	Active	(b) (4)	(b) (4)
Microcrystalline Cellulose	NF/Ph. Eur.	(b) (4)		
Lactose Anhydrous	NF/Ph. Eur.			
Croscarmellose Sodium	NF/Ph. Eur.			
Hydroxypropyl Cellulose (b) (4)	NF/Ph. Eur.			
(b) (4)	USP/Ph. Eur.			
Magnesium Stearate[d]	NF/Ph. Eur.	(b) (4)		
Filmcoating				
(b) (4) White	Company standard	(b) (4)		
(b) (4)	USP/Ph. Eur.			
		Total Tablet Weight		618.00

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.

[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous).

(b) (4)

[d] Vegetable sourced

Dissolution Method

Below is a detailed description of the development of the dissolution method.

Initial (Development) Dissolution Method Development Using (b) (4)

Medium

(b) (4)

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(b) (4)

Proposed Regulatory Dissolution Method Parameters

The parameters selected for the proposed regulatory dissolution method for the canagliflozin 100 mg and 300 mg film-coated, to-be-marketed tablets ((b) (4) tablets manufactured with (b) (4) API) are summarized in Table 16.

Table 16: Dissolution Method Parameters for Canagliflozin 100 and 300 mg Tablets

Parameter	Value
Dissolution Apparatus:	2 (Paddle)
Medium:	0.75% SLS in water
Medium Volume:	600 mL
Medium Temperature:	37.0 ± 0.5 °C
Rotation Speed:	75 rpm
Filter:	0.45 µm membrane, 25 mm diameter or equivalent
Analytical Method:	HPLC with UV detection at 240 nm

The proposed acceptance criterion is Q= (b) (4).

The proposed dissolution method will be used as a routine quality control test. The samples are analyzed by an isocratic high performance liquid chromatographic (HPLC) method with UV detection at 240 nm.

Figure 27 and Figure 28 show the mean dissolution profiles of the registration batches.

Figure 27: Mean Dissolution Profiles of the 100 mg Registration Batches

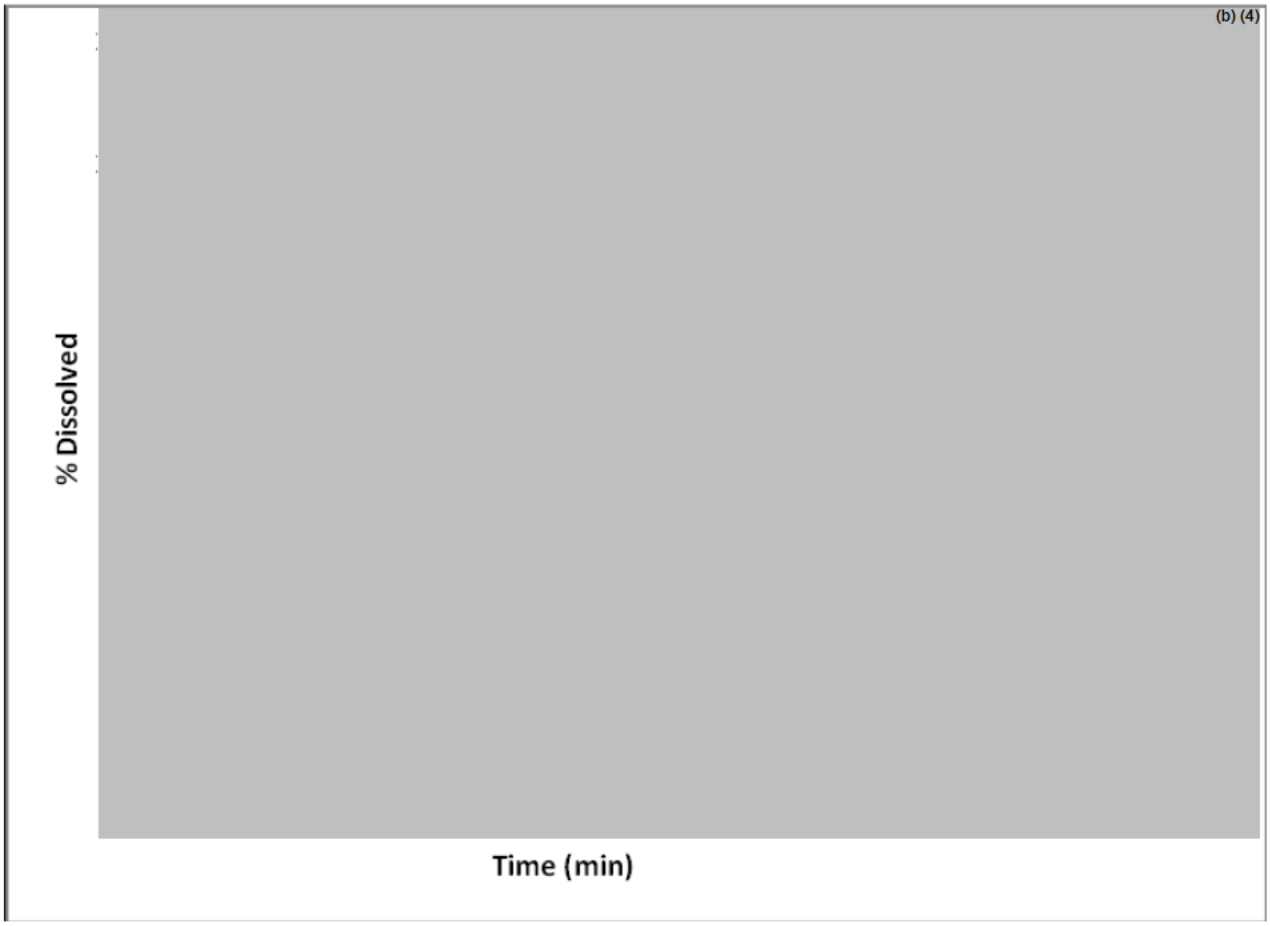


Figure 28: Mean Dissolution Profiles of the 300 mg Registration Batches

The dissolution results for clinical batches are provided in Table 17 and Table 18.

Table 17: Overview of the Dissolution Data for Clinical Batches of 100-mg Drug Product –Dissolution, n=6

	Percent Released Mean (min-max)									
Batch	10 min		20 min		30 min		45 min		60 min	
1BG3842-X	79	(b) (4)	93	(b) (4)	98	(b) (4)	99	(b) (4)	99	(b) (4)
1BG3843-X	76		93		98		99		100	
1DG4448-X	82		95		98		100		100	
1DG4449-X	78		94		98		99		100	
1DG4450-X	81		94		99		100		100	
1JG5462-X	81		94		98		100		100	
1KG5916-X	77		94		98		99		100	
1MG6386-X	81		94		98		99		100	
1MG6387-X	82		94		98		100		100	
1MG6388-X	77		93		98		100		100	

Table 18: Overview of the Dissolution Data for Clinical Batches of 300-mg Drug Product –Dissolution, n=6

	Percent Released Mean (min-max)				
Batch	10 min	20 min	30 min	45 min	60 min
1BG3847-X	78 (b) (4)	93 (b) (4)	98 (b) (4)	99 (b) (4)	100 (b) (4)
1DG4509-X	66	90	96	99	99
1DG4511-X	70	91	97	99	99
1JG5392-X	70	89	94	97	98
1JG5393-X	70	92	97	99	99
1KG5917-X	66	92	97	99	100
1MG6605-X	67	90	96	98	99
1MG6606-X	63	92	96	98	99
1MG6607-X	69	93	97	100	100
1MG6608-X	64	92	97	99	100

Dissolution data from 3 registration stability batches for each strength, stored for 12 months at 25 °C/60% RH and 30 ° C/75% RH, indicate no observable trend in the dissolution profile, as shown in Table 19 and Table 20.

Table 19: Overview of the Dissolution Data for Registration Batches of 100-mg Drug Product –Dissolution, n=6

	Percent Released Mean (min-max)				
Batch	10 min	20 min	30 min	45 min	60 min
0HG2281-X	67 (b) (4)	90 (b) (4)	95 (b) (4)	98 (b) (4)	99 (b) (4)
0HG2282-X	67	86	93	98	99
0HG2283-X	79	94	99	101	101

Table 20: Overview of the Dissolution Data for Registration Batches of 300-mg Drug Product –Dissolution, n=6

	Percent Released Mean (min-max)				
Batch	10 min	20 min	30 min	45 min	60 min
0HG2278-X	57 (b) (4)	91 (b) (4)	99 (b) (4)	102 (b) (4)	102 (b) (4)
0HG2279-X	54	87	98	100	100
0HG2280-X	46	83	96	99	100

Reviewer's Comment

The proposed dissolution method for canagliflozin 100 mg and 300 mg tablets is acceptable. However, the proposed acceptance criterion is not acceptable as the registration, clinical and stability batches release (b) (4) at 20 minutes. In addition, the Applicant did not provide comparative dissolution profiles of the debossed and non-debossed tablets.

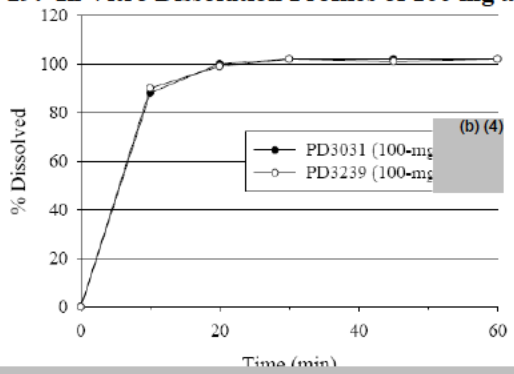
It is requested that the Applicant revise the acceptance criteria to Q = (b) (4) in 20 minutes, and submit dissolution profiles comparison between the debossed and non-debossed tablets

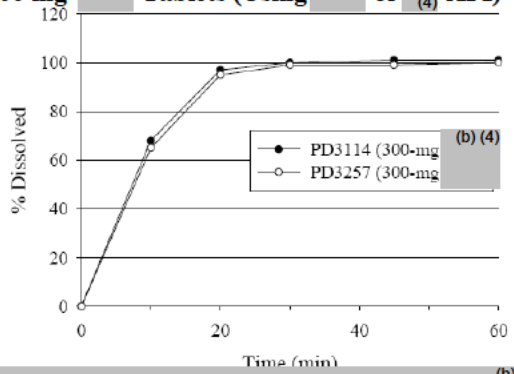
Biowaiver

Drug Substance Particle Type ((b) (4) (b) (4)

The Applicant provided comparative dissolution profiles to link (b) (4) Tablet to (b) (4) Tablet. The dissolution profiles of (b) (4) tablets using (b) (4) and (b) (4) API are similar, as shown in Figure 29. However, the dissolution profiles were obtained using the development dissolution method (b) (4)

Figure 29: In Vitro Dissolution Profiles of 100 mg and 300 mg (b) (4) Tablets (Using (b) (4) or (b) (4) API)





(b) (4)

The Applicant also studied the potential effects of drug substance particle size distribution on BA using physicochemical characteristics, GastroPlus simulations, cross-study comparison of PK data, non-clinical BA study in dogs, and population PK analysis. These studies are pending OCP and PharmTox determination.

Over-Encapsulation

Over-encapsulation was introduced for blinding purposes and used in all Phase 3 studies.

The development dissolution method with (b) (4) was used for determining the dissolution profiles of over-encapsulated and corresponding non-encapsulated tablets ((b) (4) . The Applicant stated that this method was chosen because it was more suitable for the over-encapsulated tablets. Slower dissolution was observed at the 10-minute time point for the 100 mg and 300 mg over-encapsulated tablets when compared with the non-encapsulated tablets due to over-encapsulation. Although dissolution was slower for the over-encapsulated tablet formulations at 10 minutes, dissolution was essentially almost complete by 20 minutes ((b) (4) The comparative dissolution results are provided in Table 21 and Table 22.

Table 21: Comparative Dissolution of JNJ-28431754-ZAE 100-mg Tablets and 100-mg Over-encapsulated Tablets

Dissolution Parameters: (b) (4)

(b) (4)

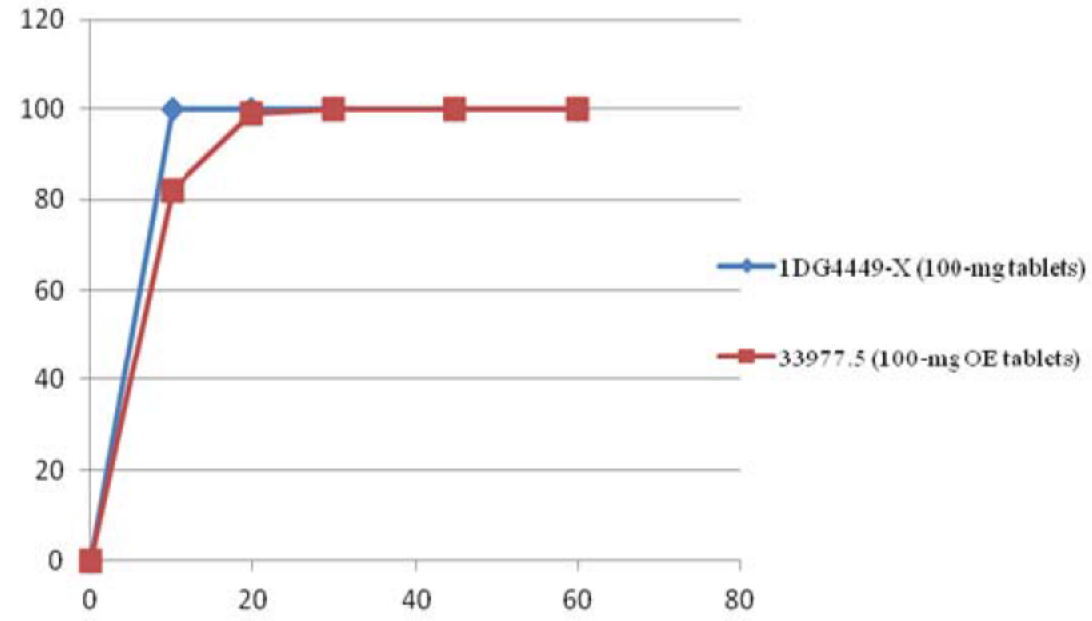
	1DG4449-X 100-mg Tablets		33977.5 100-mg OEC Tablets	
Time Points (min)	Mean (%)	Range (%)	Mean (%)	Range (%)
10	100	(b) (4)	82	(b) (4)
20	100		99	
30	100		100	
45	100		100	
60	100		100	

Table 22: Comparative Dissolution of JNJ-28431754-ZAE 300-mg Tablets and 300-mg Over-encapsulated Tablets

Dissolution Parameters: (b) (4) (b) (4)				
	OHG2279-X 300-mg Tablets		30845.14 300-mg OEC Tablets	
Time Points (min)	Mean (%)	Range (%) (b) (4)	Mean (%)	Range (%) (b) (4)
10	81		40	
20	99		92	
30	99		99	
45	99		100	
60	100		100	

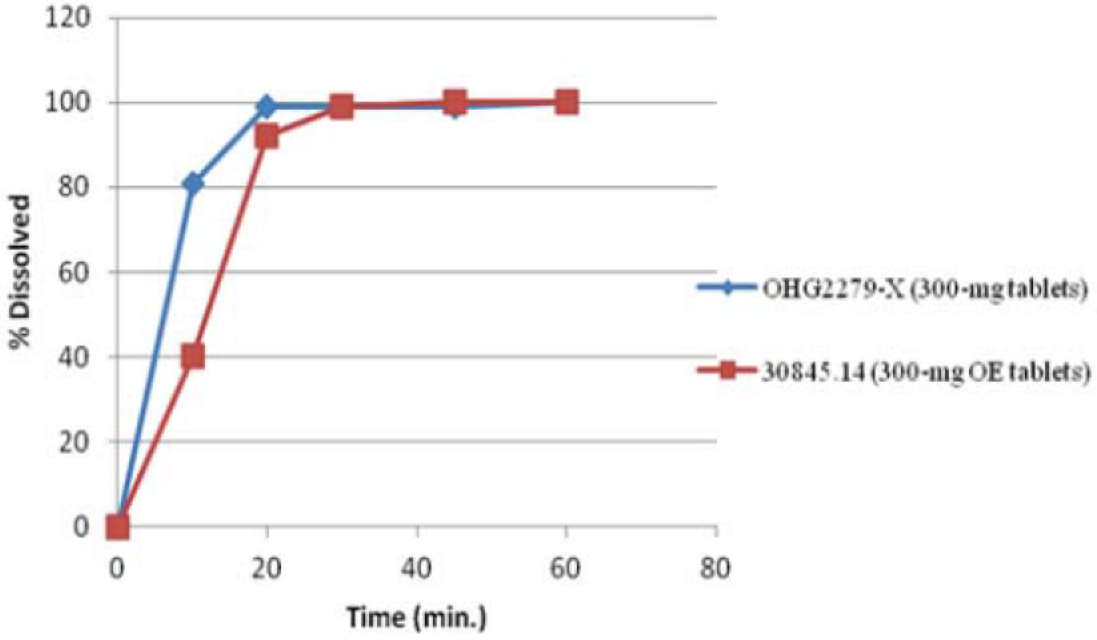
The dissolution profiles of the non-encapsulated tablets compared with the OEC tablets were comparable as shown in Figure 30 and Figure 31. The Applicant concluded that over-encapsulation of the tablets had minimal impact on the release profile of the product.

Figure 30: Comparative Dissolution for Canagliflozin Tablets and Over-encapsulated Tablets 100-mg



OE=Overencapsulated

Figure 31: Comparative Dissolution for Canagliflozin Tablets and Over-encapsulated Tablets 300-mg



OE=Overencapsulated

The Applicant also studied the effect of over-encapsulation of canagliflozin tablets on its bioavailability using clinical cross-study comparisons of PK data, and population PK analysis. These studies are pending OCP determination.

Lower Strength (100 mg)

The Applicant stated that formulation composition for the primary stability batches, the Phase 3 clinical batches, and the to-be-marketed tablets are identical. The Applicant did not conduct relative bioavailability study for the 100 tablet because (b) (4) and both strengths the 100 and 300 mg (b) (4) tablets were used in the Phase 3 studies.

Reviewer's Comment

The dissolution method used for dissolution profile comparisons between the (b) (4) tablets with (b) (4) and (b) (4) API and between the over-encapsulated and non-encapsulated tablets was the development method ((b) (4) , and not the proposed regulatory dissolution method. Therefore, the in-vitro assessment to link between ((b) (4) (b) (4) Tablet and ((b) (4) (b) (4) Tablet and between the over-encapsulated and non-encapsulated tablets is not appropriate. Thus, it is critical to evaluate the clinical cross-study comparisons of PK data and population PK analysis. The assessment is pending OCP review.

Manufacturing Site Change

The initial Phase 3 drug product clinical batches were manufactured at the clinical manufacturing facility formerly located in (b) (4) And, the batches from the proposed commercial manufacturing site in Gurabo (Puerto Rico) were used for the rest of the Phase 3 clinical batches.

Comparative dissolution data for canagliflozin tablets manufactured at the facility in (b) (4) and that in Gurabo, Puerto Rico were generated using the proposed regulatory method [600 mL of 0.75% sodium lauryl sulfate in purified water at 75 rpm using USP Apparatus 2 (paddles)]. Results for 100 mg tablets are provided in Table 23 and Figure 32. Results for 300 mg tablets are provided in Table 24 and in Figure 33.

Table 23: Comparative Dissolution of JNJ-28431754-ZAE 100-mg Tablets

Dissolution Parameters: 600 mL of 0.75% Sodium Lauryl Sulfate in Purified Water
USP Apparatus 2 (paddles) at 75 rpm

	(b) (4)	Gurabo	Gurabo	Gurabo
	PD3245 (n=12)	0HG2281-X (n=6)	0HG2282-X (n=6)	0HG2283-X (n=6)
Time Points (min)	Mean (%)	Mean (%)	Mean (%)	Mean (%)
5	26	36	29	38
10	57	67	67	79
15	78	83	80	87
20	87	90	86	94
30	94	95	93	99
45	97	98	98	101
60	99	99	99	101

Figure 32: Comparative Dissolution for Canagliflozin Tablets 100-mg

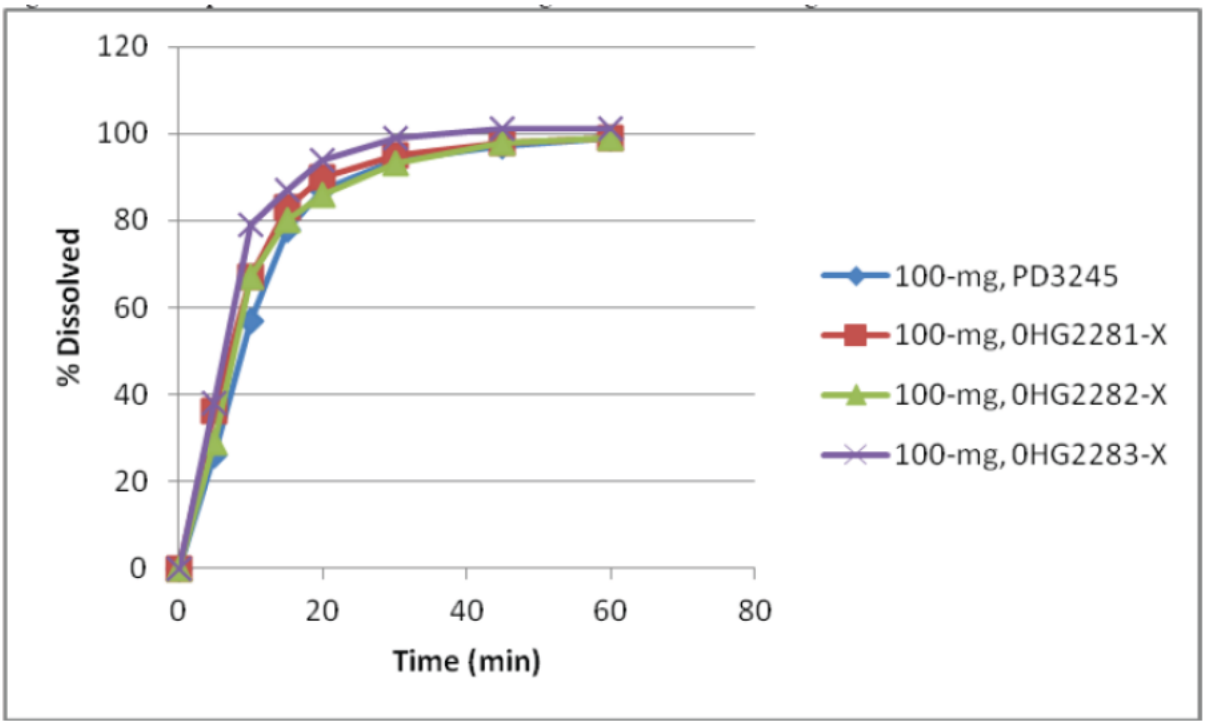
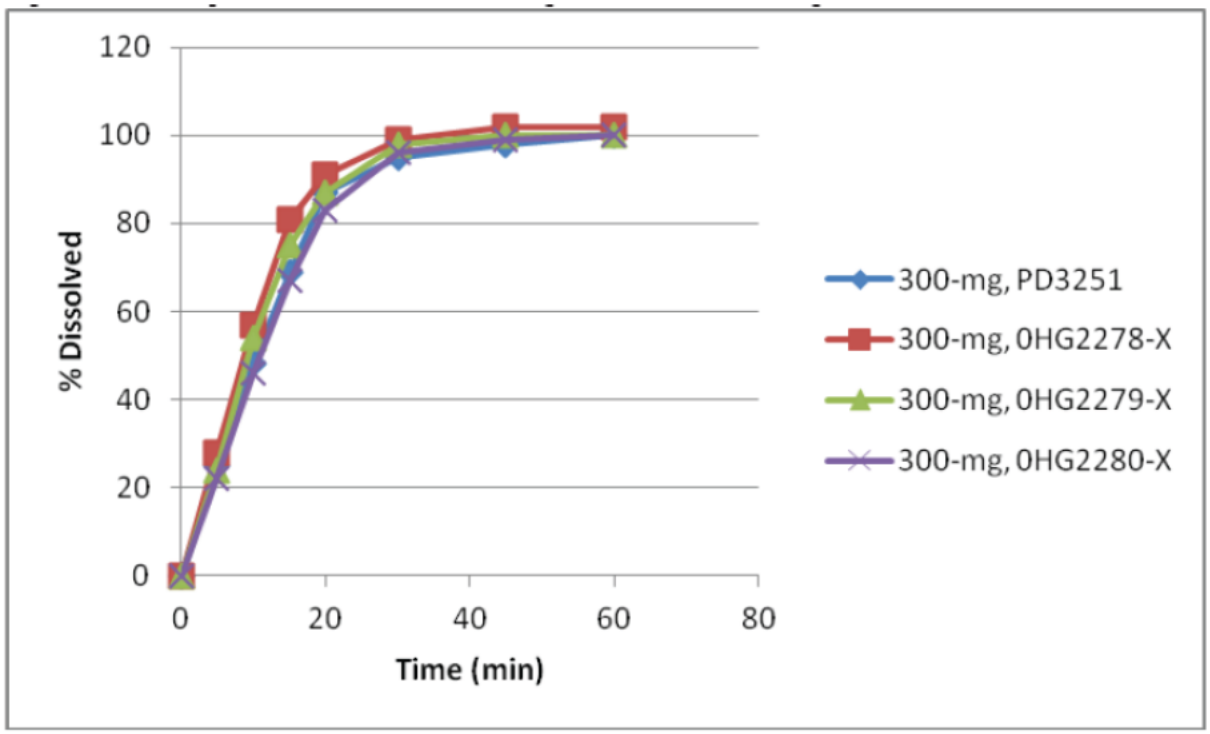


Table 24: Comparative Dissolution of JNJ-28431754-ZAE 300-mg Tablets

Dissolution Parameters: 600 mL of 0.75% Sodium Lauryl Sulfate in Purified Water USP Apparatus 2 (paddles) at 75 rpm				
	[redacted] (b) (4)	Gurabo	Gurabo	Gurabo
	PD3251 (n=12)	0HG2278-X (n=6)	0HG2279-X (n=6)	0HG2280-X (n=6)
Time Points (min)	Mean (%)	Mean (%)	Mean (%)	Mean (%)
5	25	28	24	22
10	48	57	54	46
15	69	81	75	67
20	87	91	87	83
30	95	99	98	96
45	98	102	100	99
60	100	102	100	100

Figure 32: Comparative Dissolution for Canagliflozin Tablets 300-mg



The Applicant concluded that comparative dissolution testing for tablets of both strengths manufactured at the two manufacturing sites show similar dissolution profiles for 100- and 300-mg batches.

The Applicant did not provide f2 factor calculations. The reviewer performed the f2 calculation to assess the similarity of dissolution profiles produced in the two sites. The results of the f2 calculation are shown Table 25 below.

Table 25: f2 factor Results Comparing the Clinical Batch and the Three Commercial Batches

Reference Lot	Test Lot	F2

PD 3245 (100 mg)	OHG2281-X OHG2282-X OHG2283-X	56.93 65.49 45.76
PD3251 (300 mg)	OHG2278-X OHG2279-X OHG2280-X	57.14 68.15 75.67

Reviewer's Comment
The Applicant did not provide f2 calculation results. Based on the Reviewer's calculations above, one lot of the 100 mg strength at the commercial site failed f2. All other lots made at the commercial site met the similarity factor f2 >50.

Design of Experiment (DoE)
The Applicant provided the Target Product Profile (TPP) in Table 26.

Table 26: Target Product Profile Against Which Process Development Activities Were Conducted

Quality Attribute	Target	Criticality Assessment
Dosage Form	(b) (4)	Not applicable
Potency		Related to assay and uniformity of dosage units
Pharmacokinetics		Related to dissolution
Appearance		Critical
Assay		Critical
Chromatographic Purity		Critical
Uniformity of Dosage Units		Critical
Tablet Hardness		Critical
Dissolution		Critical
Disintegration		Critical
Friability		Critical

For the manufacturing process DoE studies, (b) (4) In the main DoE study, the Applicant tested (b) (4) batches of (b) (4) tablets using (b) (4) process. Each batch was (b) (4), ranging from (b) (4) Tablet response variables included weight variation, thickness, hardness, disintegration time, friability, content uniformity, and dissolution. The target quality acceptance criteria for disintegration time of last tablet is (b) (4) and for dissolution is percent dissolved at 20 min between (b) (4). All tablets met the acceptance criteria for disintegration and dissolution, as seen in Figure 33 and Figure 34 below.

Figure 33: Disintegration Time of Tablets Manufactured at (b) (4)

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/s/

HOUDA MAHAYNI
02/01/2013

JOHN Z DUAN
02/01/2013

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	204042	**Brand Name**	INVOCANA™ (Proposed)
OCP Division (I, II, III, IV, V)	DCP II	**Generic Name**	Canagliflozin
Medical Division	DMEP	**Drug Class**	SGLT-2 inhibitor
OCP Reviewer	Manoj Khurana, Ph.D.	**Indication(s)**	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
OCP Pharmacometrics Reviewer	-	**Dosage Form**	100 mg and 300 mg tablets
OCP Team Leader	Immo Zadezensky, Ph.D. (Acting)	**Dosing Regimen**	Once daily
Date of Submission	May 31, 2012	**Route of Administration**	Oral
Estimated Due Date of OCP Review	December 31, 2012	**Sponsor**	Janssen Research & Development
PDUFA Due Date	March 31, 2013	**Priority Classification**	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	26		
I. Clinical Pharmacology				
Mass balance:	**X**	1		NAP1006
Isozyme characterization:	**X**	**7**		studies including human liver, kidney cytosol & micorsomes; hepatocytes
Blood/plasma ratio:				
Plasma protein binding:	**X**	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	3		DIA1015 (Covers proposed dose range); DIA1001; TA-7284-01 (JPN)
multiple dose:	**X**	1		DIA1030
Patients-				
single dose:				
multiple dose:	**X**	4		DIA1007, DIA1023, NAP1002, TA-7284-02 (JPN)
Dose proportionality -				

fasting / non-fasting single dose:	X			DIA1015; DIA1001
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	5		DIA1029, DIA1031, DIA1034, DIA1048, NAP1004
In-vivo effects of primary drug:	X	7		DIA1002, DIA1004, DIA1006, DIA1009, DIA1014, DIA1016, DIA1028,
In-vitro:	X	11		Potential enzyme/transporter interactions
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		DIA1003
hepatic impairment:	X	1		DIA1013
PD:				
Phase 2:	X	2		DIA1025, DIA1045
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	11		DIA1008; DIA1010 (TQT); DIA1011, DIA1019, DIA1020, NAP1005 (Photosensitivity); DIA1022; DIA1032; NAP1008; DIA2001; OBE2001
Phase 3 clinical trial:	X	3		DIA3004, DIA3005, DIA3009; Exp-resp relationships
Population Analyses -				
Data rich:	X	2		Pop-PK using rich data obtained in 9 studies and sparse data from Phase 2 and 3 studies, and Pop-PKPD (Exposure-response) analysis
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:	X	1		DIA1021
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2		DIA1017; TA-7284-03
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	5		DIA1043 (with TBM formulation); NAP1001; NAP1003; TA-7284-01; TA-7284-08
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	X			
III. Other CPB Studies				

Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies		94		

Filability		
	"X" if yes	Comments
Application filable?	X	Comments to the Sponsor: Submit the GastroPlus Model files.
Submission in Brief: See the details below.	Reviewer's Comments: None	

Submission in Brief:

The sponsor, Janssen Research & Development, has submitted a new drug application (NDA) seeking approval for INVOCANA™ (Canagliflozin). Canagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2). The low-affinity/high-capacity SGLT2 transporter in the proximal renal tubule reabsorbs the majority of glucose filtered by the renal glomerulus. Pharmacological inhibition of SGLT2 is expected to decrease renal glucose reabsorption, and thereby increase urinary glucose excretion and lower plasma glucose in patients with type 2 diabetes mellitus (T2DM). The sponsor developed Canagliflozin in collaboration with Mitsubishi Tanabe Pharma Corporation (MTPC).

Overall sponsor submitted 42 clinical pharmacology studies, 18 in vitro studies, and reports for the following:

- pharmacogenomics statistical analysis,
- population pharmacokinetic analysis,
- population PKPD (Exposure-response) analysis,
- validation of the proposed RT_G (renal threshold for glucose reabsorption) biomarker,
- GastroPlus™ Modeling (to assess the effect of API particle size on the canagliflozin exposure for the immediate release formulation), and
- 26 bioanalytical study reports.

There were changes in the formulation during the drug development;

- Tablets manufactured from (b) (4)
- (b) (4)

The to-be-marketed (TBM) formulation is the (b) (4) which was used in Phase 3. Therefore, no pivotal bridging study was conducted.

Clinical Pharmacology Review Questions:

- What is the dose-response, systemic exposure-response relationship for Canagliflozin for efficacy?

    - What is the impact of covariates (including formulation change and renal impairment) on exposure-response?
    - Does exposure-response information support the proposed dose?
- What is the systemic exposure-response relationship for Canagliflozin for safety?
    - What is the concentration-QT relationship for Canagliflozin concerning safety?
    - Does exposure-safety information support the proposed dose?
- What is the effect of food on pharmacokinetics of Canagliflozin?
    - Do the results warrant any dose adjustment?
    - Do the results support sponsor's proposed language?
    - Are analytical methods adequate?
- What is the effect of Canagliflozin on other co-administered drugs and vice-versa?
    - Does the DDI result warrant for any dose adjustments for Canagliflozin and the co-administered drugs?
    - Are analytical methods adequate?
- Are sponsor's assessments for specific populations appropriate and do they adequately support the proposed labeling language?
- What is the relative bioavailability of to-be-marketed formulation in comparison to the formulations used in the development phase?
    - Are analytical methods adequate?

The key aspects of the filing and questions for clinical pharmacology review are presented in the slides below:

Attachment 1: Clinical Pharmacology Filing Meeting Presentation

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NDA 204042 Filing Meeting

Clinical Pharmacology Perspective

INVOCANA® (Proposed)
Canagliflozin
("*CANA*")

Sponsor: Janssen Research And Development LLC
Submitted: 05/31/2012

Manoj Khurana, PhD
Office of Clinical Pharmacology

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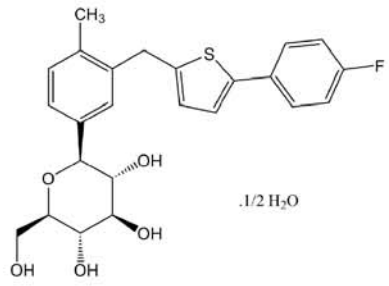
Canagliflozin: A new molecular entity



Canagliflozin

- **Class:** Inhibitor of sodium-glucose transporter 2 (SGLT2) in proximal renal tubule
- **Proposed Indication:**
  - adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- **Formulation:** film-coated oral tablets:
  - 100 mg
  - 300 mg
- **Recommended dose:**
  - 100 mg or 300 mg QD, preferably before first meal
  - Reduce dose of insulin/insulin secretagogue (e.g., SU)
  - 100 mg once daily in patients :
    - on loop diuretics,
    - with moderate RI, or
    - patients ≥ 75 years of age
  - Correct volume depletion prior to initiation
  - Escalate to 300 mg QD for additional glycemic control and if adequately tolerated

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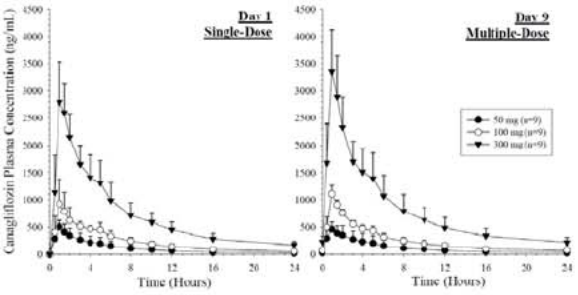
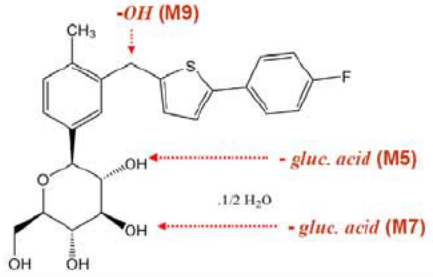
Canagliflozin ADME





- Fairly rapid absorption (tmax ~ 1 hour)
- T1/2 ~12 hours
- Absolute BA ~ 65%
- No time dependent PK
- AUC0-24 similar with QD and BID regimens for total dose of 100 mg or 300 mg
- Metabolized to inactive metabolites:
  - *O*-glucuronides M5 (~ 1.9% to 30% of total in plasma; formed by UGT2B4) and
  - M7 (16% to 29%; formed by UGT1A9)
- 60% in feces (42% intact, 7% M9, 3% M7)
- 33% in Urine (13% M5, 17% M7, <1% intact)
- Negligible chiral conversion to alpha-Anomer

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Biopharmaceutics: Formulation Development

Nature of Change	Development Phase	Clinical Trial
(b) (4)	Phase 1 and 2	• NAP1001: Food Effect • NAP1003: Rel BA and PD for 25, 200, and 400 mg (HSG vs. susp.)
		• DIA1021: Absolute BA (HSG Tablet)
		• DIA1017: Rel BA (FBG vs HSG)
	Phase 1 and 3	• GastroPlus M&S • Population PK • Cross-study comparison
	Phase 1 and 3	• DIA1043: Food Effect on TBM formulation

No pivotal BE study – to be marketed formulation was used in Phase 3

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Clinical Pharmacology Review Focus

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Summary of Clinical Pharmacology Studies

Type of Study	Number of Studies	Population	Number of Subjects
Phase 1			
Mass-Balance	1 (NAP1006)	Healthy subjects	6
Single-Dose	3 (NAP1001, DIA1001, DIA1015)	Healthy subjects	89 (48+17+24)
Multiple-Dose	3 (NAP1008, DIA1030, DIA1032)	Healthy subjects (healthy obese subjects in NAP1008)	121 (60+27+34)
	3 (NAP1002, DIA1007, DIA1023)	Subjects with T2DM	140 (93+20+27)
PD	1 (DIA1022)	Healthy subjects	24
	2 (DIA1025, DIA1045)	Subjects with T2DM	51 (14+37)
Hepatic Impairment	1 (DIA1013)	Otherwise healthy subjects with mild or moderate hepatic impairment or normal hepatic function	16
Renal Impairment	1 (DIA1003)	Otherwise healthy subjects with mild, moderate, or severe renal impairment, with end-stage renal disease, or with normal renal function	40
Non-Caucasian Subjects	3 (TA-7284-01, TA7284-02, DIA1008)	Japanese subjects (healthy and T2DM) or healthy Indian subjects	96 (30+51 +15)
Drug-Drug Interaction	12 (NAP1004, DIA1002, DIA1004, DIA1006, DIA1009, DIA1014, DIA1016, DIA1028, DIA1029, DIA1031, DIA1034, DIA1048)	Healthy subjects	248 (16+28+ 29+28+22+ 18+13+18+ 14+18+30+ 14)
QT/QTc	1 (DIA1010)	Healthy subjects	58
Photosensitivity	4 (NAP1005, DIA1011, DIA1019, DIA1020)	Healthy subjects	67 (12+25+24+ 6)
Phase 2	1 (DIA2001)	Subjects with T2DM	287
	1 (OBE2001)	Nondiabetic obese subjects	250
Phase 3	3 (DIA3004, DIA3005, DIA3009)	Subjects with T2DM	839 (160+220+459)
Total	40		2,332

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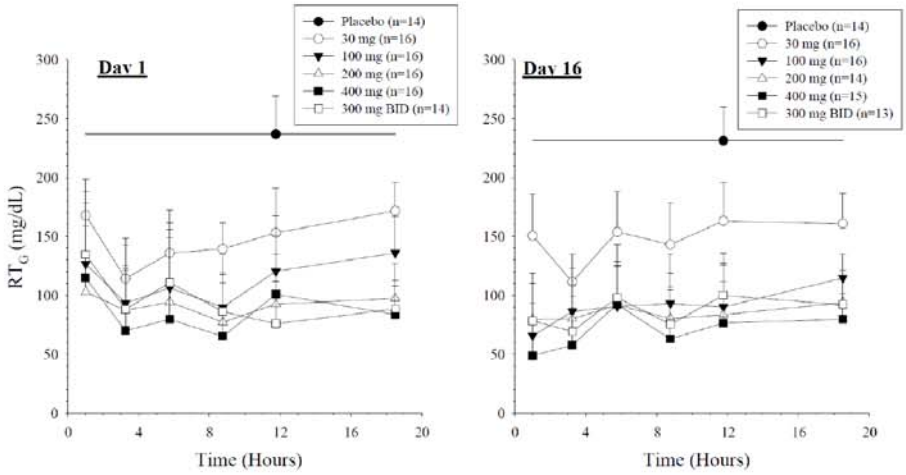
PK/PD of Canagliflozin

Sponsor proposed a new PD marker: Renal threshold for glucose excretion (RTG)



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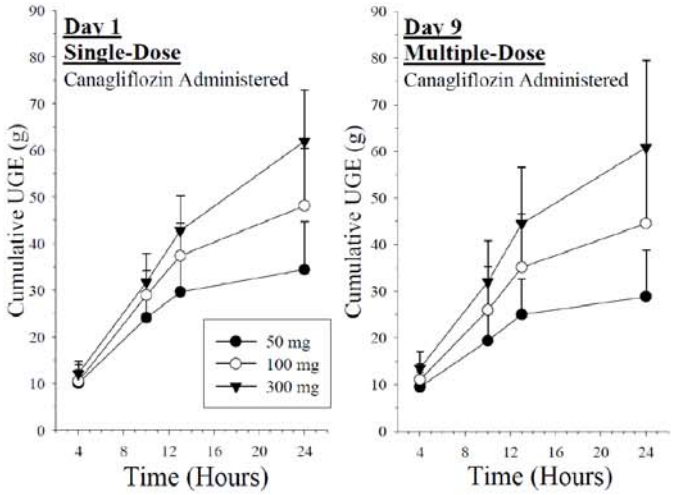
Dose-Response of Canagliflozin: Phase 1 Data

- **Sponsor:** Both UGE and RT_G show dose dependence



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Effect of Intrinsic Factors on PK

- **Sponsor:**
  - *No dose adjustment for body mass index, body weight, sex, race, and genetic polymorphisms (with respect to the UGT1A9*3 allele) based on the results of population PK analysis.*
  - *None of these covariates had clinically relevant effect on PK of CANA.*
  - *100 mg in patients ≥ 75 years of age (higher sensitivity to ADR)*
- **Review Questions:**
  - What is the impact of age (geriatrics), BMI, Gender on PK of CANA?
  - Is sponsor's proposed language in the label acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? – **Yes**

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Use in Specific Populations – Renal or Hepatic Impairment

- **Sponsor:**
  - *Renal Impairment*
    - *No dose adjustment in mild RI*
    - *100 mg QD in moderate RI*
    - *Do not use in severe RI and ESRD.*
  - *Hepatic Impairment:*
    - *No dose adjustment in mild or moderate HI*
    - *Has not been studied in severe HI*
- **Review Questions:**
  - What is the impact of renal or hepatic impairment on PK of CANA?
  - What is the impact of renal impairment on efficacy/safety of CANA (Exposure-response assessment)?
  - Is sponsor's proposed language in the label acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? – **Yes**

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Extrinsic Factors – DDI

- **Effect on CANA:**
  - *Tested rifampin, metformin, hydrochlorthiazide, OCs (EE+LEVO), probenecid, cyclosporine*
  - *Rifampin reduces AUC by 50%; consider 300 mg QD.*
- **Effect of CANA:**
  - *Tested acetaminophen, metformin, hydrochlorthiazide, OCs (EE+LEVO), digoxin, simvastatin, warfarin*
  - *No clinically relevant DDIs; no dose adjustment for these drugs*
  - *Digoxin to be adequately monitored*
- **Review Questions:**
  - What is the DDI potential of CANA and other drugs with CANA?
  - Is proposed language in label acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? **Yes**

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PK Comparability of Different Formulations

- **Sponsor:**
  - *To-be-marketed formulation used in Phase 3*
  - *Formulations* (b) (4) *are bioequivalent for PK*
  - *No clinically meaningful difference between* (b) (4)
- **Review Questions:**
  - Are sponsor's claims acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? – **Yes**

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Modeling and Simulations

- Population PK analysis
- Population PKPD analysis
- Validation of renal threshold for glucose excretion (RTG) as PD measure of SGLT2 inhibition
- GastroPlus® M&S for effect of particle size distribution on exposure
- Simcyp DDI Simulations

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Application Filability and Consults

- Yes, the application is filable from the clinical pharmacology perspective
- No OSI consults
- Request for Sponsor: GastroPlus® Model files

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 204042 **Applicant: Janssen Research & Development** **Stamp Date: 05/31/2012**

Drug Name: Canagliflozin **NDA/BLA Type: (505(b)(1))**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			BE is not pivotal as TBM formulation was used in Phase 3
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			Sponsor submitted statistical analysis report for PGx analysis
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	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)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

	need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

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.

Manoj Khurana

Reviewing Pharmacologist Date

Immo Zadezensky (Acting)

Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

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

/s/

MANOJ KHURANA
08/22/2012

IMMO ZADEZENSKY
08/22/2012