FDA Briefing Document

NDA 204042

Invokana (canagliflozin) Tablets

Applicant: Janssen Pharmaceuticals, Inc.

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

January 10, 2013

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Table of Contents

Draft Discussion Points

Cardiovascular Risk

The cardiovascular risk associated with canagliflozin use was assessed in a pre-specified meta-analysis of adjudicated cardiovascular events across nine Phase 2-3 clinical trials using an endpoint that combines cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina.

Based on the information provided in the briefing package and the presentations at today's meeting please discuss whether you believe the applicant has provided sufficient evidence of cardiovascular safety to support marketing of canagliflozin.

In your discussion address the following specific points

- Whether results based on the pre-specified Cox proportional hazards model are reliable.
- The divergence of risk estimates for the components of MACE+ in the pre-specified meta-analysis in which the HR for nonfatal stroke exceeds 1.0 while the other components are below 1.0.
- Your level of concern regarding the apparent imbalance not favoring canagliflozin in early (< 30 days) MACE+ events observed in the dedicated cardiovascular outcomes trial (DIA-3008)
- The clinical relevance of the observed changes to blood pressure, weight and low density cholesterol levels toward informing overall cardiovascular benefit/risk associated with canagliflozin use.

Benefit-Risk: Renal Impaired Population

Based on the information provided in the briefing materials and presentations at today's meeting do you believe the potential benefits of canagliflozin outweigh its potential risks when used in a population of patients with type-2 diabetes and moderate renal impairment?

In your discussion consider and comment on the following:

- The impact of renal function on the glucose-lowering effect of canagliflozin
- The impact of canagliflozin on the risk of renal function deterioration
- The clinical importance of observed volume- and electrolyte- related changes associated with canagliflozin use to the overall safety of this population
- The clinical importance of the observed increased risk of genitourinary tract infection associated with canagliflozin use to the overall safety of this population.

- The clinical importance of bone and calcium metabolism related effect associated with canagliflozin use to the overall safety of this population

Fracture Risk

In an analysis of clinical fractures across the Phase 3 development program, a numerical imbalance not favoring canagliflozin was seen in the incidence and in the exposure-adjusted incidence of fractures. The disparity appears driven by low-trauma upper limb fractures and to a lesser degree by spine fractures with little differences in lower limb, pelvis or rib fractures.

Comment on the clinical significance of this finding on your overall assessment of benefit risk balance.

In your discussion consider the following:

- The relevance of observed changes in calcium, phosphorus, parathyroid hormone and 1,25 dihydroxy vitamin D levels to this finding
- The relevance of changes to bone turnover markers to this finding
- The relevance of the bone mineral density changes to 26-weeks in the dedicated study in elderly individuals (DIA-3010) to this finding

Nonclinical Review

Application: Canagliflozin, NDA 204042
Drug Class: Sodium Glucose Transporter 2 Inhibitor (SGLT2 inhibitor)
Clinical Indication: Type 2 Diabetes
Reviewer: Fred Alavi, Ph.D., and Todd Bourcier, Ph.D., Division of Metabolism and Endocrinology Products, FDA

Background

The nonclinical evaluation of canagliflozin included studies suitable to characterize the pharmacology and toxicology of a new molecular entity intended for chronic clinical use. Long term studies included assessment of systemic toxicity in dogs for one year and in rats for six months, and assessment of carcinogenic potential in rats and mice for two years. The animal species used in these studies are relevant to assessing toxicity of canagliflozin and other SGLT2 inhibitors in general, as these compounds elicit the expected pharmacological response from inhibiting SGLT2 (e.g., glucosuria, polyuria) and, at higher doses in most cases, inhibiting SGLT1 (e.g., carbohydrate 'malabsorption', gastrointestinal disturbance). The following discussion summarizes key findings considered relevant to potential safety issues identified during clinical development and from the completed clinical program for canagliflozin.

Bone Health

Monitoring of bone health in clinical studies was in part prompted by the finding that clinically relevant doses of canagliflozin increased trabecular (cancellous) bone and decreased bone turnover in short and long-term toxicology studies conducted in rats. Trabecular accretion was most prominent in younger rats with rapidly growing bones and was reversible upon cessation of drug exposure. Despite the increase in trabecular number and volume, bone mineralization and strength were not substantially altered at clinically relevant drug exposure. Measures of bone mineralization and strength at higher doses of canagliflozin were confounded by reductions in body weight from excessive diuresis and caloric loss. No fractures were observed in the non-clinical program.

Disrupted calcium homeostasis likely underlies canagliflozin's effect on trabecular bone. Indicative of inducing a hypercalcemic state, canagliflozin consistently reduced serum (1,25)-dihydroxy vitamin D and parathyroid hormone and increased urinary excretion of calcium by several fold relative to control animals. Markers of both bone resorption (e.g., urinary deoxypyridinoline) and formation (e.g., osteocalcin) similarly declined, indicative of an overall attenuation of bone turnover. Serum calcium levels minimally changed due to these compensatory changes in calcium and bone regulatory mechanisms. Structural changes to trabecular bone were not observed in dogs or mice where alterations in calcium homeostasis were significantly less apparent than in rats. This is an important observation, as it suggests that susceptibility to trabecular accretion correlates with the degree of disrupted calcium homeostasis, and the latter is readily monitorable in the course of clinical trials.

Janssen proposes that alterations in calcium homeostasis and trabecular accretion in rats exposed to canagliflozin are related to carbohydrate malabsorption secondary to inhibition of

intestinal SGLT1. In brief, they propose that inhibiting intestinal SGLT1 reduces absorption of dietary glucose and galactose which leads to increased fermentation of these unabsorbed sugars in the distal intestine. The acidic fermentation products decrease intestinal pH, resulting in increased solubility and absorption of dietary (ionized) calcium. Osmotic pressure exerted by excessive cecal fermentation might also increase intestinal permeability and allow for greater paracellular diffusion of calcium. Janssen empirically demonstrated that intestinal absorption of dietary calcium indeed increases for the first few hours following dosing of canagliflozin in rats. Also, the effects of canagliflozin on calcium homeostasis and trabecular accretion in rats were abrogated by reducing the dietary content of calcium and by switching the carbohydrate source to fructose, a sugar that is absorbed by GLUT5 and not by SGLT1 transporters. Although canagliflozin was designed to selectively inhibit SGLT2, Janssen states that shortly after administration of the recommended clinical dose, canagliflozin may temporarily reach an intestinal concentration sufficient to inhibit SGLT1 in human subjects. This is of interest, as distal fermentation of unabsorbed sugars reportedly enhances intestinal calcium absorption and may increase bone mineralization in young adolescent human subjects (Cashman 2006; Scholz-Ahrens 2007). Markers indicative of carbohydrate malabsorption and measurements of bone quality were therefore assessed in the course of clinical trials with canagliflozin, and are described in the clinical section of the FDA background document.

Disrupted calcium homeostasis and trabecular bone accretion in toxicology species is a common finding in drug development programs for numerous SGLT1 and SGLT2 inhibitors. While the data supporting a relationship to carbohydrate malabsorption is increasingly compelling, there remain a number of compounds wherein trabecular accretion is not observed in rodents despite evidence that SGLT1 is inhibited (e.g., intestinal distension, calciuria, or intentional targeting of SGLT1). Therefore, as this mode of increased absorption of dietary calcium is functional in human subjects, trabecular bone accretion in rodents remains a clinical concern when it occurs near clinical drug exposure. However, this is amenable to monitoring in clinical trials with assessment of risk being based on the degree of change in markers of calcium homeostasis and bone turnover.

<u>Carcinogenicity</u>

As an investigational drug intended for chronic use in human subjects, the carcinogenic potential of canagliflozin was assessed in life-time (2 year) studies conducted in mice and rats. Canagliflozin did not increase the incidence of neoplasms or pre-neoplastic histological lesions in CD-1 mice at doses up to 14-times the 300mg clinical dose, based on plasma drug exposure. However, over a similar range of drug exposure, canagliflozin resulted in neoplasms of the renal tubules, adrenals, and testicular Leydig cells of Sprague-Dawley rats (Table 1). By standard testing, canagliflozin is not genotoxic and therefore the positive tumor response in rodents is postulated to occur via a non-genotoxic mode of action.

Table 1: Incidence of Neoplasms in Sprague Dawley rats administered canagliflozin *(n=65/group)*		**Canagliflozin, mg/kg**			
		0	10	30	100
Multiple of Clinical Exposure			*1-2x*	*5-7x*	*12-21x*
Adrenal Gland Pheochromocytoma, *(adenoma, carcinoma combined)*	Male	4	4	7	28*
	Female	2	1	3	7*
Kidney Renal tubule *(adenoma, carcinoma combined)*	Male	0	0	2	12*
	Female	0	0	0	8*
Testes Leydig cell adenoma	Male	1	8*	20*	24*

**statistically significant* *Data source: NDA 204042, Janssen*

Testicular Leydig cell tumors (LCT) increased at all doses of canagliflozin tested, with the lowest dose approximating clinical drug exposure. Disruption of the hypothalamus-pituitary axis leading to excess LH or LHRH stimulation of Leydig cells is a well-described mode of action that underlies most cases of Leydig cell hyperplasia and LCT in experimental rat strains (Prentice & Meikle, 1995). Human and rat Leydig cells are both responsive to LH; however, rats are considered more susceptible to endocrine-related testicular hyperplasia due to several-fold higher LH receptor expression and responsiveness to LHRH by rat compared to human Leydig cells. Changes consistent with the known mode of tumorigenic action for rat LCT were observed with canagliflozin, including a sustained increase in serum LH during a 6-month study in rats and decreased serum testosterone in the 2-year rat study. By comparison, Janssen reports that serum testosterone and LH did not change in the course of clinical trials with canagliflozin. As discussed below, carbohydrate malabsorption may also be a necessary event, but it remains unclear as to how canagliflozin alters serum testosterone and LH in rats. However, the absence of carbohydrate malabsorption and changes to LH and testosterone in human subjects minimizes the clinical relevance of LCT observed in rats.

Renal tubule neoplasms and adrenal pheochromocytoma occurred in both male and female rats, and the increased tumor incidence is unequivocally related to canagliflozin at the 100mg/kg dose, or approximately ≥12-times clinical exposure. The relatively high ≥12-fold multiple of clinical exposure associated with these tumors and the 5- to 7-fold safety margin afforded by the highest non-tumorigenic dose is interpreted as presenting a low risk that chronic exposure to canagliflozin would result in similar human cancers. Additionally, several lines of evidence (summarized below) implicate carbohydrate malabsorption and disrupted calcium homeostasis as a necessary proximal event in the proposed mode of tumorigenic action. Canagliflozin does not result in significant carbohydrate malabsorption or calcium imbalance in human subjects, and therefore would not engage this mode of tumorigenic action sufficiently to increase concern of a human adrenal/kidney cancer risk.

Several lines of evidence suggest that a state of carbohydrate malabsorption and disrupted calcium homeostasis is associated with a triad of renal, adrenal, and Leydig cell neoplasms in rodents:

- Extensive literature documents that lactose and sugar alcohols result in adrenal pheochromocytoma and LCT in rats (Sinkeldam 1992; Tischler 1996; Bar 1988). At sufficiently high doses, these poorly digestible sugars result in a carbohydrate malabsorptive state and result in disrupted calcium homeostasis (e.g., hypercalciuria, tissue and renal mineralization). Higher doses of vitamin D3 can also disrupt calcium homeostatsis but without altering carbohydrate absorption; yet, similar to lactose and xylitol, vitamin D3 increases proliferation of rat adrenal chromaffin cells (Tischler 1996). Carbohydrate malabsorption associated with disrupted calcium homeostasis is the proposed mode of tumorigenic action for these poorly digestible sugars and sugar alcohols (Roe 1989; Lynch 1996).

- Acarbose is an alpha-glucosidase inhibitor which acts by reducing the breakdown of complex sugars in the intestines, resulting in carbohydrate malabsorption and an increased cecal load of carbohydrate. Acarbose also increases the incidence of renal tubule neoplasms and LCT in Sprague Dawley rats. Reducing the pharmacodynamic effect of acarbose by either supplementing glucose as the dietary carbohydrate or by administering the drug separate from feeding prevented the increase in both renal neoplasms and LCT in the same rat strain (Precose Drug Label, Schulter 1988). This series of investigational 2-year studies demonstrated that alteration of carbohydrate absorption was a necessary proximal event in the emergence of renal and testicular neoplasms in response to acarbose.

- Janssen conducted two six-month investigational studies to explore whether carbohydrate malabsorption and disrupted calcium homeostasis contributed to the renal and adrenal neoplasms observed in rats. The first study utilized a low calcium diet to circumvent the excess absorption of dietary calcium that occurs secondary to carbohydrate malabsorption. The low calcium diet did not prevent carbohydrate malabsorption, but successfully reduced markers of excess calcium absorption in the first month, but failed to substantially prevent hypercalciuria by month 3 and 6 of the study. Further confounding the study, the low calcium diet itself increased markers of proliferation in the adrenal medulla and kidney cortex/outer medulla regardless of the presence of canagliflozin. Due to these factors, results of this study were considered unhelpful in addressing the issue. The second six-month study substituted fructose as the dietary carbohydrate. Intestinal absorption of fructose occurs via GLUT5 transport, and would not be altered by inhibition of SGLT1 by canagliflozin. Substitution with fructose prevented the increase in cecal enlargement and the change in markers of calcium homeostasis (serum PTH, hypercalciuria) throughout the entire study period, marking success of this intervention in substantially reducing carbohydrate malabsorption induced by canagliflozin. Fructose also substantially prevented the increase in cell proliferation (Brdu incorporation) observed in the adrenal medulla and renal cortex/outer medulla induced by canagliflozin. This investigational study with fructose substitution provides reasonable evidence that carbohydrate malabsorption and disrupted calcium homeostasis are necessary proximal events in the pathway leading to renal and adrenal neoplasms in SD rats exposed to canagliflozin.

The profile of tumor responses in rodents to SGLT2 inhibitors as a new therapeutic drug class is beginning to emerge. Among five investigational SGLT2 inhibitors that have filed final or interim

findings from rodent carcinogenicity studies with the Agency, four have reported neoplasms of the renal tubules, adrenal gland, or testicular Leydig cells. The single agent that did not observe tumors in these tissues nonetheless reported an increased incidence of atypical hyperplasia of the renal tubules. Of interest, the tumor response is now observed in two species, mice and rats, discounting earlier speculation that this phenomenon is specific to rats. A common observation among the compounds listed in Table 2 is evidence of carbohydrate malabsorption and disrupted calcium balance, albeit to a varying extent depending on the pharmacology and kinetics specific to each compound.

Table 2: Neoplasms associated with SGLT2 inhibitors in rodents

	Tumor sites		
Drug	**Renal Tubules**	**Adrenal gland**	**Testicular Leydig**
Canagliflozin	✓	✓	✓
Drug A	✓ (mice)		
Drug B	✓ (mice)	✓	✓ (mice & rats)
Drug C		✓	✓
Dapagliflozin*	none (atypical hyperplasia)	none	none

** From FDA and BMS briefing documents, Advisory Committee for NDA 202293 (July 2011)*

Carbohydrate malabsorption and calcium imbalance appear to be key proximal events in the tumorigenic mode of action of SGLT2 inhibitors. This supports an approach whereby the clinical relevance of pre-neoplastic and neoplastic responses in rodents to SGLT2 inhibitors is assessed on a case-by-case basis, with the existence of a safety margin and the presence or absence of these key events in clinical trial participants being primary considerations. For canagliflozin, significant carbohydrate malabsorption or calcium imbalance did not occur in human trials, and a safety margin exists for the renal tubular and adrenal malignancies observed in rats.

References

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Precose© Product Labeling appr. 2/29/12 (original approval Sept 1995; www.drugs@fda.gov)

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CLINICAL PHARMACOLOGY REVIEW

Office of Clinical Pharmacology

Prepared by Manoj Khurana, PhD and Jayabharathi Vaidyanathan, PhD

Canagliflozin Pharmacokinetics (PK)

Following oral administration, peak plasma concentrations of canagliflozin are reached within 1 hour. The absolute oral bioavailability of canagliflozin is 65%. Canagliflozin exhibits dose-proportional PK in the dose range of 50-300 mg. Following once daily administration of 100 mg and 300 mg doses, steady-state plasma concentrations of canagliflozin are attained in 4-5 days. Canagliflozin is metabolized to inactive glucuronide metabolites, M7 and M5 by UGT1A9 and UGT2B4 enzymes, respectively. Canagliflozin is extensively (99%) bound to plasma proteins. In healthy adults, approximately 33% of an orally-administered dose is excreted in urine, most as metabolites (0.8% as unchanged drug and 32% as metabolites) and 60% is excreted in feces. The elimination half-life ($t_{1/2}$) of canagliflozin is approximately 12 hours.

Effect of Renal Impairment on Pharmacokinetics/Pharmacodynamics (PK/PD) of Canagliflozin:

The applicant conducted a single dose PK and PD study (Study DIA1003) in subjects with normal renal function and with different degrees of renal impairment as determined by creatinine clearance (CLCR). Later, sponsor amended the original study report with reanalysis of the data by classifying the subjects into renal function groups based on estimated glomerular filtration rate (eGFR) using MDRD equation. The renal function categories in this analysis were:

- Normal renal function (eGFR $\geq$ 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 on dialysis)

All subjects received a single 200 mg canagliflozin dose. Subjects with ESRD received a single dose either pre-dialysis or post-dialysis (with 10 days between treatments).

The mean elimination $t_{1/2}$ of canagliflozin was slightly longer in subjects with mild, moderate, and severe renal impairment (22.8, 17.5, and 23.9 hours, respectively) and in subjects with ESRD (pre-dialysis group, [21.4 hours], post-dialysis group [17.2 hours]) compared to the subjects with normal renal function (14.2 hours). Geometric mean values for systemic exposure of canagliflozin (AUC_{inf}) were about 15%, 29% and 53% higher in subjects with mild, moderate and severe renal impairment groups, respectively, compared

to the normal renal function group. The exposure in subjects with ESRD was comparable to the normal group. Contrary to AUC, mean canagliflozin C_{max} values in all the renal impairment categories were lower than in the normal group (Figure 1).

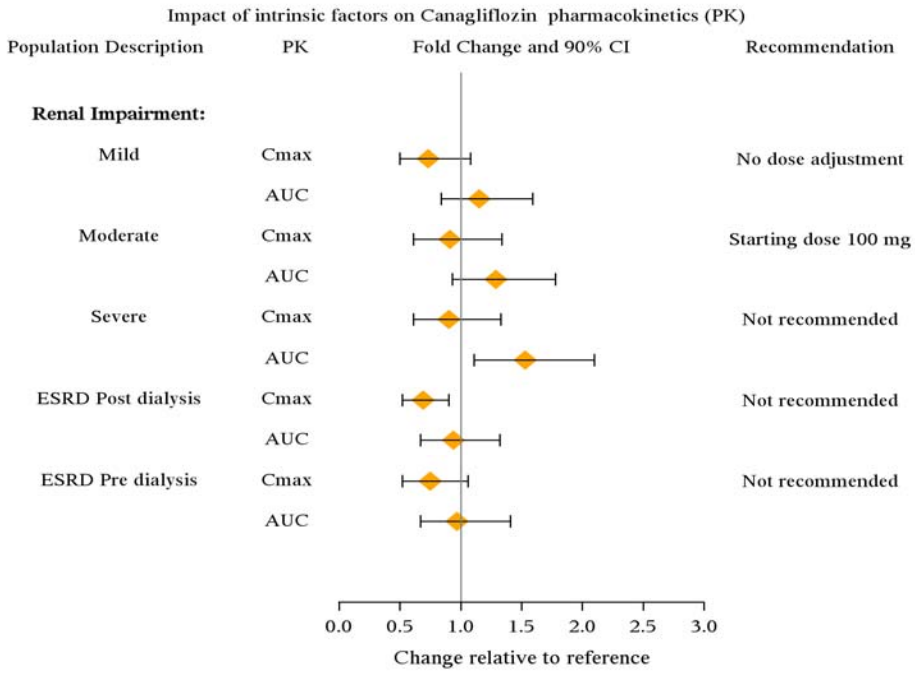

Figure 1: Canagliflozin plasma AUC and Cmax fold changes and 90% confidence interval in renal impairment groups compared to the normal renal function group.

The exposure of major glucuronide metabolites of canagliflozin, M7 and M5 also increased in renal impairment as shown in Table 1.

Table 1: Percent increase in plasma AUC of canagliflozin glucuronide metabolites, M7 and M5 in renal impairment as compared to normal renal function subjects

Metabolite	Mild	Moderate	Severe	ESRD	
				Pre-dialysis	Post-dialysis
M7	3%	127%	71%	69%	64%
M5	31%	172%	195%	160%	190%

Despite the higher systemic exposure of canagliflozin in subjects with moderate and severe renal impairment, the 24-hour glucosuric effect decreased progressively. Across all renal function groups, canagliflozin treatment increased urinary glucose excretion at 24 hours (UGE_{0-24h}) relative to baseline. However, the extent of the increase in UGE_{0-24h} from baseline was substantially reduced in patients with decreased eGFR as compared to normal renal function subjects (Figure 2). Further, for canagliflozin less reduction in renal threshold for glucose excretion (RT_{G}) was observed with increasing severity of renal

impairment. 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, whereas in subjects with moderate or severe renal impairment, the 24-hour mean RTG was approximately 86 mg/dL and 96 mg/dL, respectively.

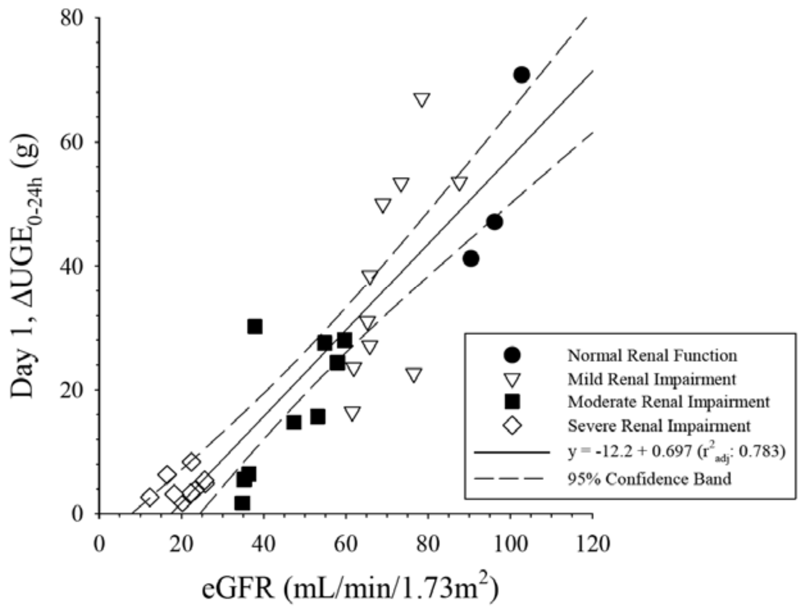

Figure 2: UGE0-24h changes from baseline (Day -1) versus eGFR in subjects with varying degrees of renal function after single 200 mg oral dose of canagliflozin
Source: Sponsor's clinical study report addendum DIA1003

The applicant has proposed no dose-adjustment of canagliflozin in mild renal impaired subjects and a starting dose of 100 mg for the moderate renal impaired subjects. They are proposing that the drug be not recommended for use in severe and ESRD subjects.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Efficacy: Statistical Review

CLINICAL STUDIES

NDA/BLA #:	NDA 204042
Drug Name:	Canagliflozin (proposed tradename INVOCANA)
Indication(s):	Treatment of patients with type 2 diabetes mellitus
Applicant:	Janssen Research & Development, LLC
Date(s):	May 31, 2012
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Wei Liu, Ph.D.
Concurring Reviewers:	J. Todd Sahlroot, Ph.D. (Deputy Director)
Medical Division:	Metabolism and Endocrinological Products (HFD-510, DMEP)
Clinical Team:	Hyon Kwon, PharmD, MPH Jean-Marc Guettier, M.D. (Team Leader)
Project Manager:	Jena Weber

Table of Contents

LIST OF TABLES

1 Clinical Data

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 submitted NDA 204042 on May 31, 2012 for canagliflozin (proposed tradename INVOCANA) tablets for the treatment of patients with type 2 diabetes mellitus. The sponsor submitted 9 phase 3 efficacy and safety studies evaluating canagliflozin in T2DM patients (Table 1).

Table 1. Overview of Phase 3 Trials

Study	Phase and Design	Treatment Period*	Follow-up Period*	Treatment arms (n)	Study Pop baseline HbA1c (%)
Monotherapy		26 weeks	26 weeks		
DIA3005 Main study	R,DB,PC, PG			Placebo 192 CANA 100 mg 195 CANA 300 mg 197	≥7 to ≤10
High Glycemic substudy	R,DB,PC	26 weeks	NA	CANA 100 mg 47 CANA 300 mg 44	>10 to ≤12
Add-on to AHA Monotherapy					
DIA3006 Add-on to metformin	R,DB,PC, AC,PG	26 weeks	26 weeks	Placebo 183 CANA 100 mg 368 CANA 300 mg 367 Sitaglipin 100mg 366	≥7 to ≤10.5
DIA3009 Add-on to metformin	R,DB,AC, PG	52 weeks	52 weeks	CANA 100 mg 483 CANA 300 mg 485 Glimepiride ↑6/8 mg 482	≥7 to ≤9.5
Add-on to Dual Combination AHA Therapy					
DIA3002 Add-on to metformin + sulfonylurea	R,DB,PC, PG	26 weeks	26 weeks	Placebo 156 CANA 100 mg 157 CANA 300 mg 156	≥7 to ≤10.5
DIA3012 Add-on to metformin + pioglitazone	R,DB,PC, PG	26 weeks	26 weeks	Placebo 115 CANA 100 mg 113 CANA 300 mg 114	≥7 to ≤10.5
DIA3015 Add-on to metformin + sulfonylurea	R,DB,AC, PG	52 weeks	NA	CANA 300 mg 377 Sitagliptin 100 mg 378	≥7 to ≤10.5
Special Population					
DIA3010 older adults (≥55 to ≤80 years of age)	R,DB,PC, PG	26 weeks	78 weeks	Placebo 237 CANA 100 mg 241 CANA 300 mg 236	≥7 to ≤10

DIA3004 Moderate renal impairment (eGFR ≥ 30 to <50 mL/min)	R,DB,PC, PG	26 weeks	26 weeks	Placebo 190 CANA 100 mg 90 CANA 300 mg 89	≥7 to ≤10.5
DIA3008					
Sulphonylurea substudy[1]	R,DB,PC, PG	18 weeks	NA	Placebo 45 CANA 100 mg 42 CANA 300 mg 40	≥7 to ≤10.5
Insulin substudy[2]	R,DB,PC, PG	18 weeks	NA	Placebo 565 CANA 100 mg 566 CANA 300 mg 587	≥7 to ≤10.5

* Treatment period denotes the duration to primary endpoint and the follow-up period the extension duration
Note: AC = active-controlled, AHA = anti-hyperglycemic agent, CANA = canagliflozin, DB = double-blind, eGFR = estimated glomerular filtration rate, PC = placebo-controlled, PG = parallel group, R = randomized.
[1] Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of the stratification used for randomization) reviewed
[2] Population 2 (all subjects randomized to Strata 1, 2 and 3 who were taking insulin ≥30 units per day at study entry) reviewed

2 Evaluation of Efficacy

I evaluated the efficacy of canagliflozin in nine Phase 3 studies designed to establish the efficacy and safety of canagliflozin as monotherapy, as add-on therapy to other anti-hyperglycemic agent (s), and in special populations.

The primary endpoint for all Phase 3 studies was the change in HbA1c from baseline to the end of the study.

Major secondary endpoints included
- changes from baseline to the end of the study in FPG
- changes from baseline to the end of the study in 2-hour post-meal glucose
- proportion of subjects achieving an HbA1c target (<7.0%) at the end of the study
- percent change from baseline to the end of the study in body weight,
- percent change from baseline to the end of the study in HDL-C
- percent change from baseline to the end of the study in fasting triglycerides
- percent change from baseline to the end of the study in systolic blood pressure

The sponsor defined the following analysis sets for the evaluation of efficacy:
- Modified intent-to-treat (mITT): All randomized subjects who took at least 1 dose of double-blind study drug (primary analysis set)
- Per protocol: All mITT subjects who completed the required period of treatment for the primary endpoint, were not initiated on rescue therapy (ie, documented in the eCRF by the investigator) prior to the visit for the primary endpoint, and had no major protocol deviations within this treatment period.

- Completers: All mITT subjects who completed the required period of double-blind treatment for the primary endpoint, and were not initiated on rescue medication (documented in the eCRF by the investigator) prior to the visit for the primary endpoint.

The primary efficacy analysis for analyzing HbA1c was based on the mITT analysis set. This reviewer did not address statistical results for secondary endpoints.

The sponsor's pre-specified primary analysis of HbA1c used an analysis of covariance (ANCOVA) model using the last observation carried forward method (LOCF) for missing observations. In general, the ANCOVA model included terms for treatment and randomization stratification factor(s) (if applicable) as fixed effects and the corresponding baseline HbA1c value as a covariate. In Study DIA3004, an additional covariate of baseline eGFR was included in the model. Least-squares (LS) mean treatment differences between each canagliflozin group and the comparator (either placebo or active comparator) and their two-sided 95% confidence intervals (CI) were estimated from the model for each individual study.

I performed supportive analyses using the Per Protocol analysis set. As an additional supportive analysis, change from baseline in HbA1c was analyzed using mixed model repeated measures (MMRM). The MMRM analysis was based on observed data and included the fixed, categorical effects of treatment, stratification factors, visit, and treatment-by-visit interaction as fixed effects and the corresponding baseline HbA1c value as a covariate. An unstructured covariance was used to model the within-patient errors.

In the two non-inferiority studies (DIA3009 and DIA3015), a non-inferiority margin of 0.3% was used for comparisons of canagliflozin with sitagliptin after 52 weeks of treatment (DIA3015) and canagliflozin vs. glimepiride after 52 weeks of treatment (DIA3009).

For each Phase 3 study, a pre-specified sequential testing procedure by the sponsor was applied to testing the treatment differences of the primary and major secondary efficacy endpoints, to control the family-wise error rate at 5%. Each study followed a pre-specified testing hierarchy, and in some studies, the testing proceeded to testing 2 families of tests using the Hochberg procedure for endpoints of SBP, HDL-C, TG, and HOMA2-%B (DIA3012 only), conditional upon the statistical significance of the prior test(s). The sequences varied with each study, depending on whether the study was placebo-controlled, active-controlled, or a study in a special population.

2.1 Efficacy of Individual Studies

There were 9 Phase 3 studies that evaluated the efficacy of canagliflozin. The key efficacy findings reported by the sponsor were generally consistent with FDA analyses. The primary efficacy findings by the Agency are shown in Table 2.

Table 2. Primary Efficacy Results (HbA1c) for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes (Phase 3 Studies) (mITT/LOCF)

Study (Weeks)	Treatment arm	n	Baseline Mean ± SE	LSMean change ± SE	Cana minus control (95% CI)	p-value
Monotherapy						
DIA3005 (26) Main study	Cana 300 mg Cana 100 mg Placebo	193 191 189	8.01 ± 0.07 8.06 ± 0.07 7.97 ± 0.07	-1.03 ± 0.06 -0.77 ± 0.06 0.14 ± 0.06	-1.16 (-1.34, -0.99) -0.91 (-1.09, -0.73)	<.0001 <.0001
DIA3005 (26) High Glycemic	Cana 300 mg Cana 100 mg	43 46	10.62 ± 0.15 10.59 ± 0.13	2.56±0.22 -2.13±0.22		
Add-on to AHA Monotherapy						
DIA3006 (26) Add-on to metformin	Cana 300 mg Cana 100 mg Placebo	360 365 181	7.95 ± 0.05 7.94 ± 0.05 7.96 ± 0.07	0.94 ± 0.04 -0.79 ± 0.04 -0.17±0.06	-0.77(-0.91,-0.64) -0.62 (-0.76,-0.48)	<.0001 <.0001
DIA3009 (52) Add-on to metform	Cana 300 mg Cana 100 mg Glimepiride ↑6/8 mg	474 478 473	7.79 ± 0.04 7.78 ± 0.04 7.83 ± 0.04	-0.93 ± 0.04 -0.82 ± 0.04 -0.82 ± 0.04	-0.12 (-0.22, -0.02) -0.01 (-0.11, 0.09)	0.0158 0.8074
Add-on to Dual Combination AHA Therapy						
DIA3002 (26) + metformin + sulfonylurea	Cana 300 mg Cana 100 mg Placebo	152 155 150	8.13 ± 0.08 8.13 ± 0.07 8.12 ± 0.07	-1.06 ± 0.08 -0.85 ± 0.08 -0.13 ± 0.08	-0.92 (-1.11, -0.73) -0.71 (-0.90, -0.52)	<.0001 <.0001
DIA3012 (26) + metformin + pioglitazone	Cana 300 mg Cana 100 mg Placebo	112 113 114	7.84 ± 0.09 7.99 ± 0.09 8.00 ± 0.09	-1.03 ± 0.07 -0.89 ± 0.07 -0.26 ± 0.07	-0.76 (-0.95, -0.57) -0.62 (-0.81, -0.44)	<.0001 <.0001
DIA3015 (52) + metformin + sulfonylurea	Cana 300 mg Sitagliptin 100mg	365 374	8.13 ± 0.05 8.12 ± 0.05	-0.66 ± 0.05 -1.03 ± 0.05	-0.37 (-0.50, -0.25)	<.0001
Special Population						
DIA3010 (26)[1] older adults	Cana 300 mg Cana 100 mg Placebo	229 239 232	7.69 ± 0.05 7.77 ± 0.05 7.76 ± 0.05	-0.73 ± 0.06 -0.60 ± 0.06 -0.03 ± 0.06	-0.70 (-0.84, -0.57) -0.57 (-0.71, -0.44)	<.0001 <.0001
DIA3004 (26)[2] Moderate renal impairment	Cana 300 mg Cana 100 mg Placebo	89 88 87	7.97 ± 0.09 7.89 ± 0.10 8.02 ± 0.10	-0.44 ± 0.09 -0.32 ± 0.09 -0.03 ± 0.09	-0.42 (-0.65, -0.19) -0.29 (-0.53, -0.06)	0.0004 0.0131
DIA3008 (18) Sulphonylurea substudy[3]	Cana 300 mg Cana 100 mg Placebo	39 40 40	8.28 ± 0.16 8.29 ± 0.13 8.49 ± 0.18	-0.79 ± 0.15 -0.70 ± 0.15 0.04 ± 0.15	-0.83 (-1.24, -0.42) -0.74 (-1.14, -0.33)	0.0001 0.0005
DIA3008 (18) Insulin substudy[2]	Cana 300 mg Cana 100 mg Placebo	572 551 545	8.27 ± 0.04 8.34 ± 0.04 8.24 ± 0.04	-0.72 ± 0.03 -0.63 ± 0.03 0.02 ± 0.03	-0.74 (-0.82, -0.65) -0.65 (-0.74, -0.56)	<.0001 <.0001

[1] ≥55 to ≤80 years of age [2] eGFR ≥ 30 to <50 mL/min
[3] population 1 [4] population 2

All superiority comparisons of canaglifozin 300 mg and 100 mg doses vs placebo were significant in all studies indicating consistency in results across different populations. The results in Table 2 based on LOCF were consistent with sensitivity analyses using MMRM.

In Study DIA3009, canaglifozin 100mg and 300mg were shown to be non-inferior to Glimepiride 6 to 8 mg at 52 weeks using a non-inferiority margin of 0.3% for HbA1c. Canagliflozin 300 mg was also shown to be statistically superior to glimepiride (p=0.016) although the treatment difference was relatively small (-0.12%).

In Study DIA3015, canagliflozin 300mg was shown to be non-inferior to sitagliptin 100 mg at 52 weeks using a non-inferiority margin of 0.3%. Canagliflozin 300 mg was also shown to be superior to sitagliptin ($p < 0.001$) based on an observed treatment difference of -0.37%.

In Study DIA3004 in patients with moderate renal impairment, canagliflozin 100mg and 300mg were both statistically superior to placebo. The HbA1c effect sizes vs placebo were modest in this population, -0.42% for 300mg and -0.29% for 100 mg. Effect sizes for subgroups based on baseline eGFR (< 45 vs > 45 mL/min/1.73 m^2) were found to be not statistically different (interaction $p > .10$).

There was a modest dose response for canaglifozin. Depending on the particular population, canagliflozin 300 mg showed additional 0.1% to 0.25% reductions in HbA1c over canagliflozin 100 mg.

2.2 Efficacy of Integrated Data

2.2.1 Integrated Analysis of HbA1c in Patients with Moderate Renal Impairment

To provide information on the efficacy of canagliflozin in a larger group of T2DM subjects with moderate renal impairment, a prespecified objective was to evaluate the changes in the primary endpoint HbA1c in a population of subjects with a baseline eGFR of ≥30 to <60 mL/min/1.73m^2 selected from the placebo-controlled Phase 3 studies that permitted enrollment of subjects with an eGFR in this range, including DIA3004, DIA3005 (excluding High Glycemic substudy), DIA3008 (all subjects including SU and Insulin substudies), and DIA3010. In DIA3008, subjects with eGFR ≥30 mL/min/1.73 m^2 were eligible to participate; subjects with an eGFR of ≥50 mL/min/1.73 m^2 were eligible for participation in DIA3005 and DIA3010. The sponsor's reported findings were identical to the results by the FDA statistical reviewer as shown below in Table 3. Analyses were stratified by study.

Table 3. HbA1c Results for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes with Moderate Renal Impairment (eGFR ≥30 to <50 mL/min) (mITT/LOCF)

Endpoint	Placebo		Canagliflozin			
			100 mg		300 mg	
HbA1c (%)	n		n		n	
eGFR ≥30 to 50 mL/min/1.73 m^2						
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	356	7.98 ± 0.05 -0.14 ± 0.06	326	8.09 ± 0.05 -0.52 ± 0.06 -0.38 (-0.50, -0.26)	354	8.07 ± 0.05 -0.62 ± 0.06 -0.47 (-0.59, -0.35)
eGFR < 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	108	8.10 ± 0.09 0.05 ± 0.19	118	8.08 ± 0.09 -0.18 ± 0.19 -0.23 (-0.45, -0.01)	122	8.10 ± 0.08 -0.34 ± 0.19 -0.39 (-0.61, -0.17)
eGFR ≥ 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	248	7.98 ± 0.06 -0.10 ± 0.07	208	8.11 ± 0.06 -0.57 ± 0.07 -0.47 (-0.61, -0.32)	232	8.10 ± 0.06 -0.62 ± 0.07 -0.52 (-0.67, -0.38)

These findings, which include data from Studies DIA3004, DIA3005, DIA3008 and DIA3010, were similar to the findings of DIA3004 alone. Subjects with lower eGFR values at baseline (< 45 mL/min/1.73 m^2) had smaller mean treatment differences than subjects with higher eGFR values at baseline (≥ 45 mL/min/1.73 m^2). The difference in effects sizes between the renal subgroups was not statistically significant (interaction p > .10).

2.2.2 Integrated Analysis of HbA1c by Age Subgroups in All Patients in Placebo-Controlled Studies

Subgroups analyses (stratified by study) of HbA1c were conducted based on pooled patient populations from placebo-controlled studies. Subgroups were defined by age category (< 65 vs > 65 years of age, and < 75 vs > 75 years of age).

There were two integrated placebo-controlled datasets. The first one (PC-1) submitted by the sponsor consisted of the overall pooled population of placebo-controlled studies and comprised subjects from the mITT analysis sets of DIA3005 Main Study, DIA3006 (excluding sitagliptin), DIA3008 SU sub-study (Population 1), DIA3002, DIA3012, and the DIA3008 Insulin sub-study (Population 2). The sponsor's reported findings were identical to FDA analyses on this pooled dataset and are shown in Table 4. The other dataset (PC-2) consisted of PC-1 and subjects from the mITT analysis sets of DIA3004 (subjects with moderate renal impairment) and DIA3010 (older adults, ≥55 to ≤80 years of age). The efficacy findings from PC-2 are shown in Table 5.

Table 4. HbA1c Results for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes (Integrated Placebo-Controlled Studies, PC-1)

Endpoint	Placebo		CANA 100 mg		CANA 300 mg	
	n		n		n	
A1C (%), All patients						
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	1191	8.11 ± 0.03 -0.15 ± 0.02	1404	8.14 ± 0.02 -0.84 ± 0.02 -0.69 (-0.75, -0.63)	1419	8.11 ± 0.02 -0.98 ± 0.02 -0.83 (-0.89, -0.77)
A1C (%), < 65 years old	n		n		n	
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	836	8.18 ± 0.03 -0.15 ± 0.03	1004	8.16 ± 0.03 -0.87 ± 0.03 -0.72 (-0.79, -0.65)	1008	8.11 ± 0.03 -1.02 ± 0.03 -0.87 (-0.94, -0.80)
A1C (%), ≥ 65 years old	n		n		n	
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	355	7.95 ± 0.04 -0.11 ± 0.04	400	8.10 ± 0.04 -0.72 ± 0.04 -0.61 (-0.72, -0.50)	411	8.09 ± 0.04 -0.85 ± 0.04 -0.74 (-0.84, -0.63)
A1C (%), < 75 years old						
Baseline mean ± SE Adj. % Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	1143	8.12 ± 0.03 -0.15 ± 0.02	1345	8.14 ± 0.03 -0.84± 0.02 -0.69 (-0.75, -0.63)	1351	8.12 ± 0.03 -1.00 ± 0.02 -0.85 (-0.91, -0.78)
A1C (%), ≥ 75 years old						
Baseline mean ± SE Adj. % Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	48	7.86 ± 0.12 -0.13 ± 0.14	59	8.13 ± 0.12 -0.77± 0.12 -0.65 (-0.96, -0.33)	68	7.87 ± 0.09 -0.68 ± 0.12 -0.55 (-0.85, -0.26)

Table 5. HbA1c Results for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes (Integrated Placebo-Controlled Studies, PC-1 + DIA3004 and DIA3010)

Endpoint	**Placebo**		CANA 100 mg		CANA 300 mg	
	n		n		n	
A1C (%), All patients						
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	1510	8.05 ± 0.02 -0.11 ± 0.02	1731	8.08 ± 0.02 -0.76 ± 0.02 -0.65 (-0.70, -0.59)	1737	8.04 ± 0.02 -0.90 ± 0.02 -0.79 (-0.84, -0.74)
A1C (%), < 65 years old	n		n		n	
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	1009	8.13 ± 0.03 0.10 ± 0.03	1167	8.12 ± 0.03 -0.80 ± 0.03 -0.70 (-0.77, -0.63)	1184	8.06 ± 0.03 -0.96 ± 0.03 -0.85 (-0.92, -0.79)
A1C (%), ≥ 65 years old	n		n		n	
Baseline mean ± SE Adj. Mean Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	501	7.89 ± 0.04 -0.12 ± 0.04	564	7.89 ± 0.04 -0.65 ± 0.03 -0.54 (-0.63, -0.45)	553	8.00 ± 0.04 -0.77 ± 0.04 -0.66 (-0.75, -0.57)
A1C (%), < 75 years old						
Baseline mean ± SE Adj. % Change from baseline±SE Cana−P, adjusted LS Mean (95% CI)	1429	8.06 ± 0.02 -0.11 ± 0.02	1629	8.09 ± 0.02 -0.77 ± 0.02 -0.66 (-0.71, -0.60)	1636	8.05 ± 0.02 -0.92 ± 0.02 -0.81 (-0.86, -0.75)
A1C (%), ≥ 75 years old						
Baseline mean ± SE Adj. % Change from baseline±SE Cana−P, adjusted LS Mean (95% CI	81	7.88 ± 0.09 -0.19 ± 0.10	102	7.94 ± 0.09 -0.65 ± 0.09 -0.46 (-0.70, -0.23)	101	7.89 ± 0.07 -0.67 ± 0.10 -0.48 (-0.71, -0.24)

For both datasets, older subjects (≥65 or ≥75 years of age) had smaller treatment differences than younger subjects (<65 or <75 years of age). The differences between subgroups were statistically significant for dataset PC-2 (interaction p-values < .10) but not for dataset PC-1 (interaction p-values > .10).

Efficacy Summary

All superiority comparisons of canaglifozin 300 mg and 100 mg doses vs placebo in HbA1c change from baseline, the primary efficacy endpoint, were significant in all studies. The results were based on LOCF as the primary method for accounting for missing data. Analyses using MMRM were consistent with the primary results with LOCF.

Canagliflozin (both doses) was shown to be non-inferior to glimepiride in Study DIA3009 and to sitagliptin in Study DIA3015. Both studies used pre-specified non-inferiority margins of 0.3%. In Study DIA3009, Canagliflozin 300 mg was also shown to be superior to glimepiride (p=0.016) although the mean treatment difference was small (-0.12%).

In Study DIA3004 in patients with moderate renal impairment, canagliflozin 100mg and 300mg were both statistically superior to placebo. Mean effect sizes vs placebo were modest in this population, -0.42% for 300mg and -0.29% for 100 mg. Effect sizes for subgroups defined by baseline eGFR (< 45 vs > 45 mL/min/1.73 m^2) were not statistically different (interaction $p > .10$).

Canagliflozin exhibited a modest dose response. Depending on the particular population, canagliflozin 300 mg showed additional 0.1% to 0.25% mean reductions in HbA1c over canagliflozin 100 mg.

Analyses of HbA1c by subgroups defined by eGFR at baseline based on integrated datasets were consistent with the results in Study DIA3004 alone. In the integrated analyses, subjects with lower eGFR values at baseline (< 45 mL/min/1.73 m^2) had smaller treatment differences than subjects with higher eGFR values at baseline (≥ 45 mL/min/1.73 m^2). The difference in effects between the subgroups was not statistically significant (interaction $p > .10$).

Subgroup analyses were conducted based on two different age cutoffs, 65 and 75 years of age. Analyses of HbA1c by age subgroups based on integrated datasets showed that older subjects (≥65 or ≥75 years of age) had smaller mean treatment differences than younger subjects (<65 or <75 years of age). The statistical evaluation of observed subgroup differences produced results that were not consistent across the two datasets of interest. Age-by-treatment interaction p-values were statistically significant for dataset PC-2 (both interaction p-values < .10) but not for dataset PC-1 (both interaction p-values > .10).

Clinical Review

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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NDA 204042: Canagliflozin

Applicant: Janssen Research and Development, LLC.

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Center for Drug Evaluation and Research

United States Food and Drug Administration

Table of Contents

Table of Tables

Table of Figures

1 Introduction

1.1 Product Description

Canagliflozin is an orally active, competitive, reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2). The applicant is seeking an indication for use of canagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Inhibition of sodium-glucose co-transport to lower hyperglycemia represents a new pharmacological target in the management of subjects with type 2 diabetes mellitus. There are currently no approved SGLT2 inhibitors and canagliflozin would be a first-in-class agent if approved.

In healthy individuals, glucose is freely filtered at the glomerulus and 100% of the filtered glucose is reabsorbed in the proximal tubule of the nephron. Two sodium glucose co-transporters (SGLTs) play an important role in renal glucose reabsorption: SGLT1 and SGLT2. SGLT2 is expressed in the proximal tubule of kidney and is responsible for the majority of glucose reabsorption. SGLT1 is also expressed in the proximal tubule and participates to a lesser extent in renal tubular glucose reabsorption.

SGLT1 is highly expressed on the brush border membrane of enterocytes where it plays an important role in intestinal glucose and galactose absorption. *In vitro*, canagliflozin was demonstrated to be 160-fold more selective for SGLT2 than for SGLT1.

Inhibition of SGLT2 reduces renal reabsorption of filtered glucose, induces an osmotic diuresis and increases urinary glucose excretion. The glycosuric effect of canagliflozin results in lowering plasma glucose levels in subjects with T2DM.

Unlike most other approved non-insulin anti-diabetic drugs currently indicated for the treatment of T2DM, the direct glucose lowering effect of canagliflozin does not depend on augmenting endogenous insulin secretion or on improving insulin sensitivity. It does however depend on the ability to excrete glucose in the urine which is in turn correlated to both plasma glucose levels and to glomerular filtration rate. As a result, the glucose lowering effect of canagliflozin is expected to wane with diminished renal function.

The applicant proposes to market a 100 and a 300 mg dose of canagliflozin to be taken once daily before the first meal of the day. A starting dose of 100 mg daily is proposed for: patients on a loop diuretic, patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73m^2), or patients who are greater or equal to 75 years of age because these subgroup of patients were observed to be at higher risk for volume depletion-related adverse reactions in the clinical program. The applicant proposes uptitration of 100 mg to 300 mg daily in these subgroups if additional glycemic control is needed. Because it would not be effective, canagliflozin would not be used in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2), end stage renal disease, or in patients on dialysis.

After ingestion, canagliflozin is rapidly absorbed, with the median time to reach maximal concentration (t_{max}) of 1 to 2 hours post-dose. Steady state is reached after 4 to 5 days of daily dose with canagliflozin 100 mg to 300 mg. Canagliflozin is extensively bound to plasma proteins (98 to 99%), mainly to albumin (97%), and as a result is negligibly removed by dialysis. *O*-glucuronidation is the major metabolic pathway for canagliflozin. The mean terminal plasma half-life ($t_{1/2}$) of canagliflozin was 10.6 and 13.1 hours with 100 mg and 300 mg dose respectively.

1.2 Description of Clinical Trial Development

Canagliflozin is being developed globally by Janssen Research & Development, LLC (JRD), except in Japan, Taiwan, and Indonesia, where the sponsor's partner, Mitsubishi Tanabe Pharma Corporation (MTCP), is conducting an independent development program. Studies conducted by MTPC are preceded by a "TA" identifier, and all the other studies are conducted by JRD. For trials sponsored by MTCP, the sponsor provided brief summary of the primary efficacy and safety results in the ISE and ISS respectively and a copy of the translated Clinical Study Reports.

The clinical program for canagliflozin consisted of:

- 40 Phase 1 trials (i.e., 35 Phase 1 clinical pharmacology and 5 biopharmaceutic trials)
- 3 Phase 2 trials, and
- 9 Phase 3 trials

Nine controlled Phase 3 trials provided pivotal efficacy and safety data for canagliflozin used as monotherapy and in combination with approved antihyperglycemic agents (AHA) in patients with T2DM for a range of clinical use scenarios.

Three Phase 3 trials evaluated use of canagliflozin in special populations of subjects with type 2 diabetes which were:

- Older adults (Trial DIA3010),
- Subjects with moderate renal impairment (Trial DIA3004), and
- Subjects with or at high risk for cardiovascular (CV) disease (Trial DIA3008).

Seven of the nine Phase 3 trials had placebo or active-controlled (sitagliptin 100 mg) double-blind extensions beyond the primary efficacy endpoint and were still ongoing at the time of NDA submission.

Therefore, data up to the primary efficacy endpoint (at the end of core double-blind period) was locked and analyzed for these seven trials, and data from the double-blind extension period have not been unblinded or analyzed at the time of the NDA submission. In addition, CV trial (DIA3008) was still ongoing, and an interim analysis with a data cutoff date of September 15, 2011 was provided.

Table 1 summarizes the key characteristics of the design, study population, treatment allocation and duration for the Phase 2b and 3 trials in the canagliflozin program.

Table 1: Phase 2b and 3 Trials in T2DM in the Canagliflozin Development Program

Trial	Trial Design	Trial Population	Treatment Groups[a] & Number of Subjects Randomized	Duration
Phase 2b Dose-Range Finding Trials				
DIA2001 Add-on to Metformin	Randomized, double-blind, placebo and active-controlled, double-dummy, parallel group, dose-ranging trial	HbA1c 7 to 10.5% inclusive	Cana 50 mg QD: 64 Cana 100 mg QD: 64 Cana 200 mg QD: 65 Cana 300 mg QD: 64 Cana 300 mg BID: 65 Sitagliptin 100 mg QD: 65 Placebo QD: 65	12 weeks
TA-7284-04 Monotherapy	Randomized, double-blind, placebo-controlled, parallel group	HbA1c 6.5 to 9.5% inclusive	Cana 50 mg: 82 Cana 100 mg: 74 Cana 200 mg: 76 Cana 300 mg: 75 Placebo: 75	12 weeks
Phase 3 Glycemic Efficacy Trials				
DIA3005 Monotherapy				
Main Study [b]	Randomized, double-blind, placebo-controlled, 3-arm parallel group	HbA1c 7 to 10% inclusive	Cana 100 mg: 195 Cana 300 mg: 197 Placebo: 192	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
High Glycemic Cohort	Randomized, double-blind, 2-arm parallel group	HbA1c >10% to ≤12%	Cana 100 mg: 47 Cana 300 mg: 44	26 weeks
DIA3006 [b] Add-on to Metformin	Randomized, double-blind, placebo- and active-controlled, 4-arm parallel group	T2DM subjects on metformin; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 368 Cana 300 mg: 367 Sitagliptin 100 mg: 366 Placebo: 183	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
DIA3009 Add-on to Metformin	Randomized, double-blind, active-controlled, 3-arm parallel group	T2DM subjects on metformin; HbA1c 7 to 9.5% inclusive	Cana 100 mg: 483 Cana 300 mg: 485 Glimepiride: 482	104 weeks (52-week active-controlled, core double-blind period plus a 52-week active-controlled, extension double-blind period)
DIA3002 Add-on to Metformin + SU	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 157 Cana 300 mg: 156 Placebo: 156	52 weeks (26-week placebo-controlled, core double-blind period plus a 26-week placebo-controlled, extension double-blind period)
DIA3012[b] Add-on to Metformin + Pioglitazone	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on metformin + pioglitazone therapy; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 113 Cana 300 mg: 114 Placebo: 115	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
DIA3015 Add-on to Metformin + SU	Randomized, double-blind, active-controlled, 2-arm parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10.5% inclusive	Cana 300 mg: 377 Sitagliptin 100 mg: 378	52 weeks
Special Population Trials				
DIA3004 Moderate Renal Impairment Study	Randomized, double-blind, placebo-controlled, 3-arm parallel group	HbA1c 7 to 10.5% inclusive; eGFR ≥30 to <50 mL/min/1.73m^2	Cana 100 mg: 90 Cana 300 mg: 89 Placebo: 90	52 weeks (26-week placebo-controlled, core double-blind period plus a 26-week placebo-controlled, extension double-blind period)
DIA3010 Older Adults	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects with 55 to 80 years of age, inclusive; HbA1c 7 to 10% inclusive	Cana 100 mg: 241 Cana 300 mg: 236 Placebo: 237	104 weeks (26-week placebo-controlled, core double-blind period plus a 78-week placebo-controlled, extension double-blind period)

DIA3008 **CV Study** (Interim Safety)	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on currently available AHA; Have a history or high risk of CV disease; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 1445 Cana 300 mg: 1441 Placebo: 1441	Event-driven
Glycemic Efficacy[c] Insulin Substudy	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on insulin ≥20 units/day as monotherapy or in combination with other AHA(s); HbA1c 7 to 10.5% inclusive	Cana 100 mg: 566 Cana 300 mg: 587 Placebo: 565	18 weeks
SU Substudy	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on SU monotherapy; HbA1c 7 to 10.5% inclusive	Cana 100 mg: 42 Cana 300 mg: 40 Placebo: 45	18 weeks

[a]Except for dose-ranging Phase 2b trial DIA2001, canagliflozin and placebo/active treatment in all other Phase 2 and 3 trials were given once daily.
[b]In these trials, subjects assigned to placebo were switched to sitagliptin during the double-blind extension period (In DIA3006, subjects randomized to sitagliptin remained on sitagliptin during the extension period)
[c]A third DIA3008 substudy was planned (add-on to pioglitazone + metformin), but there was inadequate enrollment to assess efficacy or safety
Abbreviations: Cana=canagliflozin; SU=sulfonylurea; AHA=antihyperglycemic agent; CV=cardiovascular; QD=daily; BID=twice daily
Source: Modified from ISE, Table 1

At the 4-Month Safety Update (4MSU), four of seven Phase 3 trials with controlled extension were completed (DIA3005, DIA3002, DIA3006, DIA3012), and the extension period of the remaining three Phase 3 trials are still ongoing (DIA3009, DIA3010, DIA3004). The 120 day safety update had a data cutoff date of July 1, 2012.

1.3 Study Design

Study Objectives

The stated objective of all Phase 3 trials was to assess the effect of canagliflozin relative to comparator (placebo or active) on the change in HbA1c from baseline to the primary assessment timepoint (26 or 52 weeks) and to assess the safety and tolerability of canagliflozin.

Secondary objectives across Phase 3 trials were to compare the effect of canagliflozin and comparator across other measures of glycemia (i.e., change from baseline in FPG and 2-hour PPG, proportion of subjects with HbA1c <7%) and across the following non-glycemic endpoints: body weight, systolic blood pressure, and fasting plasma lipids. For trials with controlled extension, the effect of canagliflozin relative to comparator on change in glycemic control (i.e., HbA1c and FPG) and other endpoints were also assessed at the end of extension period.

In addition to assessing the efficacy and safety of canagliflozin relative to placebo in T2DM subjects with moderate renal impairment, DIA3004 (Moderate Renal Impairment Study) also assessed change in renal function as a key secondary objective.

For DIA3010 (Older Adults Study), key secondary objective included assessing the effect of canagliflozin relative to placebo on the change in bone mineral density at the lumbar spine, hip, and distal forearm as measured by dual-energy X-ray absorptiometry (DXA) at the primary assessment timepoint and at the end of controlled extension; markers of bone turnover was also assessed at the primary assessment timepoint.

The primary objective for DIA3008 was to evaluate the effects of treatment with canagliflozin compared to placebo on important CV events (MACE), and to assess the safety and tolerability of canagliflozin. The secondary objective was to assess the safety and tolerability of canagliflozin. Within DIA3008, two substudies focused on the glycemic efficacy and safety of canagliflozin in T2DM subjects on specific background AHAs (e.g., insulin and SU).

Overview of Study Design:

All Phase 3 trials were multinational, randomized, double-blind, parallel-group trials.. The 52-week placebo-controlled Phase 3 trials (DIA3002, DIA3004, DIA3005, DIA3006, and DIA3012) and 104-week placebo-controlled Phase 3 trial DIA3010 assessed the primary efficacy endpoint at Week 26. The active comparator-controlled Phase 3 trials DIA3009 (104-week) and DIA3015 (52-week) assessed the primary efficacy endpoint at Week 52. The CV safety trial DIA3008 included two efficacy sub-studies evaluating canagliflozin as an add-on to sulfonylurea (SU) monotherapy and insulin with primary efficacy endpoint measured at Week 18. All the placebo-controlled trials were designed to show superiority of canagliflozin compared to placebo, whereas two active-controlled trials (DIA3009 and DIA3015) were designed to show non-inferiority to active comparator.

For trials DIA3002, DIA3005 [Main Study], DIA3006, DIA3009, DIA3012, and DIA3015 where canagliflozin was added to a specific baseline regimen of anti-hyperglycemic agent(s) (AHA), eligible subjects already receiving protocol-specified AHA therapy at required doses at screening directly entered a 2-week, single-blind, placebo run-in period after 1-week screening period. Subjects not on trial specific background AHA therapy and/or protocol-specified dose entered an 8-12 week run-in period for AHA dose adjustment, which included a washout/dose titration (as necessary) and dose stable period. Subjects who met trial specific background AHA therapy at protocol-specified doses and enrollment HbA1c level at the end of the AHA adjustment period entered the 2-week single-blind, placebo run-in period. For trials with metformin as the required background AHA, a dose of ≥2000 mg/day, or ≥1500 mg/day for those with intolerance, was required. For trials with sulfonylurea as the required background AHA, the dose was to be ≥50% of the maximum labeled dose.

For trials of special population (DIA3004, DIA3008 and its sub-studies, and DIA3010), subjects were not required to be on a specific background regimen for treatment of their diabetes; canagliflozin was added to their background stable AHA(s). Two substudies of DIA3008 evaluated canagliflozin as add-on to subjects already on a stable dose of insulin and sulfonylurea monotherapy.

In all trials except DIA3015, CV trial (DIA3008), and sub-studies (DIA3005 High Glycemic sub-study and DIA3008 sub-studies), subjects who completed the primary assessment at the end of double-blind core period continued the trial in a double-blind extension. In DIA3015 and DIA3005 High Glycemic sub-study, the trials were completed after the primary assessment at Week 52 and Week 26 respectively. DIA3008 is an event-driven trial. The duration of the double-blind extension period was 26 weeks for DIA3002, DIA3004, DIA3005 (Main Study), DIA3006, and DIA3012, 52 weeks for DIA3009, and 78 weeks for DIA3010. Subjects received the same double-blind study treatment during subsequent double-blind extension period in all

trials except for subjects assigned to the placebo group in trials DIA3005 (Main Study), DIA3006, and DIA3012 who were switched, in a blinded fashion, to sitagliptin 100 mg daily during the controlled extension period.

Randomization, Stratification, Treatments, and Blinding:

For all Phase 3 trials, subjects who met enrollment criteria at the end of the placebo run-in period were randomly assigned to double-blind treatment on Day 1. Randomization to double-blind treatment was stratified in all Phase 3 trials according to the stratification variables shown in Table 2. All trials included treatment arms for both proposed doses of canagliflozin, 100 mg and 300 mg daily except for one trial, DIA3015, which included only canagliflozin 300 mg daily dose group. Sitagliptin 100 mg daily was the active comparator group in DIA 3006 and DIA3015, and glimepiride (titrated to 6 mg daily) was the active comparator in DIA3009.

Table 2: Stratification Variables in Phase 2 and 3 Trials

Table 5 : Stratification Variables in Efficacy Analysis Models of the Phase 2 and 3 Double-Blind Studies

Study	Stratification
Phase 2b Dose-Range Finding	
DIA2001 Add-on to Metformin	No Stratificaion
Phase 3 Glycemic Efficacy Studies	
DIA3005 **Main Study** Monotherapy	(1) Taking AHA(s) (2) Participate in FS-MMTT procedure
High Glycemic Cohort	(1) Taking AHA(s)
DIA3006 Add-on to Metformin	(1) Metformin monotherapy / metformin in combination with an SU
DIA3009 Add-on to Metformin	(1) Metformin dose stabilization/AHA washout (2) Country
DIA3002 Add-on to Metformin + Sulfonylurea	(1) AHA adjustment period (2) Participate in FS-MMTT procedure
DIA3015 Add-on to Metformin+ Sulfonylurea	(1) Week -2 $HbA_{1c} \geq 9\%$ (2) Participate in FS-MMTT procedure
DIA3012 Add-on to Metformin + Pioglitazone	(1) AHA adjustment period (2) Pioglitazone dose (30/45 mg)
DIA3010 Older Subjects (ie, ≥55 to ≤80 years of age) /Body Composition Study	(1) T-score of lumbar spine (< -1.5 or ≥ -1.5) (2) Pioglitazone.
DIA3004 Renal Study	(1) Atherosclerotic cardiovascular disease (2) AHA adjustment period
DIA3008[e] CV Safety Study	Six predefined strata based upon background AHA medication(s) [§]
The six strata in DIA3008 are based on: insulin monotherapy or insulin with other oral antihyperglycemic agent, sulfonylurea, PPARγ agonist and any antihyperglycemic agent	

Source: ISE Statistical Analysis Plan, Attachment 1.1, Table 5

Treatment allocation was blinded to investigators, center personnel, subjects, and sponsor staff involved in the trial. HbA1c, FPG, and PPG values were masked to study centers after

randomization unless criterion for glycemic rescue therapy was met or glycemic rescue therapy had been started. To prevent unblinding, UGE results were also not given to the investigational centers, and the central laboratory urinalysis did not include the measurement of urine glucose.

For each Phase 3 trial, the database was locked at each trial's predefined primary assessment (e.g., after all subjects completed the core double-blind treatment period or were discontinued before this period). The trial was unblinded only by the sponsor to complete the CSR, and others remained blinded to treatment assignment until the trials are completed for trials that included a double-blind extension period (e.g., all subjects complete the double-blind extension period or discontinue from trial), and a separate database lock will occur when all randomized subjects complete the trial or are discontinued. The extension period of all seven Phase 3 trials with extensions were still ongoing at the time of NDA submission.

Study Populations: Canagliflozin was evaluated in subjects on specific background treatments for diabetes, which included diet and exercise (DIA3005), single oral AHAs (metformin in DIA3006 and DIA3009, sulfonylurea in DIA3008 sulfonylurea sub-study), dual combination of AHAs (metformin+SU in DIA3002 and DIA3015, and metformin+pioglitazone in DIA3012), or on insulin (DIA3008 insulin substudy). Other Phase 3 trials investigated canagliflozin in subjects who were on a wide range of AHAs with moderate renal impairment (DIA3004), older adults (DIA3010), and subjects with or high risk for CV disease (DIA3008).

Key Inclusion Criteria:

- Subjects were eligible if their T2DM was inadequately controlled at screening and at the start of placebo run-in period while on protocol-specified background AHA therapy, with HbA1c of 7 to 10.5% inclusive at screening (for those not requiring AHA adjustment period) or at the start of placebo run-in period (for those requiring AHA adjustment period to meet the protocol-specified diabetes therapy), except for:
    - DIA3005 (main monotherapy study) and DIA3010 (Older Adults Study), subjects were eligible if their HbA1c was 7 to 10% inclusive;
    - DIA3005 High Glycemic substudy, subjects were eligible if their HbA1c was >10% and ≤12%;
    - DIA3009, subjects were to have HbA1c 7 to 9.5% inclusive.
- FPG value <270 mg/dL at the start of placebo run-in period, except for DIA3015 and DIA3005 High Glycemic substudy which required FPG ≤300 mg /dL and ≤350 mg /dL respectively. At the time of randomization (Day 1), subjects were also required to have fasting fingerstick glucose of ≥110 mg/dL.
- Adults with 18 to 80 years of age inclusive, except for trials of canagliflozin in special populations:
    - For DIA3004 (Moderate Renal Impairment Study), the age requirement was ≥25 years without upper limit of age;
    - For DIA3008 (Cardiovascular Safety Study), the age requirement was ≥30 years with CV history or ≥50 years with CV risk factors without upper limit of age;
    - For DIA3010 (Older Adults Study), the age requirement was 55 to 80 years inclusive.

- Both men and women were eligible for enrollment in all Phase 3 trials. Women were excluded if they were pregnant or breastfeeding but could participate if they were postmenopausal, surgically sterile, or practicing birth control.
    - For DIA3010 (Older Adults Study), only women who had been postmenopausal for at least 3 years were allowed to participate. This criteria ensured that participants were beyond the period of rapid estrogen decline, which could have confounded the detection of drug related effects on bone density endpoints.
- For trial DIA3010 only: Subjects with a baseline BMI of 20 to 40 kg/m^2 due to concerns regarding the quality of bone imaging techniques in subjects with BMI of >40 kg/ m^2.
- For trial DIA3004 only: Subjects were to have moderate renal impairment, as defined by eGFR values (estimated by the 4-variable MDRD equation) ≥28 and ≤55 mL/min/1.73m^2 at the prescreening/screening visit and ≥30 and ≤50 mL/min/1.73m^2 at the Week -2 visit (about 4-week interval), with generally stable renal function, as demonstrated by ≤25% decline in eGRF at Week -2 relative to (pre)screening value.

<u>Key Exclusion Criteria</u>:

- Metabolic Conditions:
    - History of diabetic ketoacidosis, type 1 diabetes mellitus, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy;
    - One or more severe hypoglycemic episode(s) (requiring help of another person) within 6 months of screening.
- Renal disease and function:
    - Requiring treatment with immunosuppressive therapy or history of dialysis or renal transplant;
    - Following exclusion based on renal function:
        - In trials of canagliflozin as add-on to metformin (alone or in combination with other AHA: DIA3002, DIA3006, DIA3009, DIA3012, and DIA3015), subjects with a screening eGFR <55 mL/min/1.73 m^2 (<60 mL/min/1.73 m^{2}for countries where metformin labels contraindicated <60 mL/min/1.73 m^2) or serum creatinine ≥1.4 mg/dL for men and ≥1.3 mg/dL for women;
        - For DIA3005 and DIA3010, screening eGFR <50 mL/min/1.73 m^2;
        - For DIA3008, severe renal impairment (eGFR <30 mL/min/1.73 m^2); for subjects taking metformin, serum creatinine ≥1.4 mg/dL for men and ≥1.3 mg/dL for women;
    - For DIA3004, presence of nephrotic syndrome (e.g., severe proteinuria with hypoalbuminemia and/or edema) or inflammatory renal disease (e.g., acute interstitial nephritis, acute or rapidly-progressive glomerulonephritis), or likely need for dialysis or transplantation during the trial period.
- Cardiovascular disease:
    - History of MI, unstable angina, revascularization, or cerebrovascular accident within 3 months of screening, planned revascularization procedure, or history of New York Heart Association Class 3-4 cardiac disease (Class 4 only in DIA3008);
    - Uncontrolled hypertension.

- Laboratory Values:
    - Fasting serum triglycerides ≥600 mg/dL at screening
    - Alanine aminotransferase level >2x the upper limit of normal (ULN) or total bilirubin >1.5x the ULN at screening
- History of hepatitis B surface antigen or hepatitis C antibody positive or other clinically active liver disease
- For trial DIA3010 only: Subjects on bisphosphonates within 12 months of screening, lumbar spine T scores of <-2.5 at screening, and/or those with illnesses that may confound assessment of bone density (i.e., rheumatoid arthritis, bone diseases, inherited bone disorders, non-healed fractures, etc).

Study Visits and Efficacy Measurements: The schedule of efficacy measurements during the double-blind period up to the primary endpoint are summarized in Table 3 for the nine Phase 3 trials.

Table 3: Efficacy Time and Events Schedule for Phase 3 Trials

Procedures and Evaluations Related to Efficacy[a]	Rand.	Double-blind Treatment Period up to Primary Assessment Timepoint						
	Day 1	Wk 6 or 8	Wk 12	Wk 18[a]	Wk 26[a]	Wk 34 or 36[a]	Wk 42 or 44[a]	Wk 52[a]
Laboratory assessment								
HbA_{1c}	All	All but 3008	All	All	All but 3008	3009, 3015	3009, 3015	3009, 3015
FPG	All	All[b]	All	All	All but 3008	3009, 3015	3009, 3015	3009, 3015
Fasting C-peptide	All but 3004			3008	All but 3004, 3008, and 3015			3009, 3015
Fasting insulin and proinsulin	3005, 3009, 3008, 3015			3008	3005, 3009, 3010			3015
Fasting lipids	All			3008	All but 3008			
Free fatty acid	3005				3005			
Procedures								
MMTT	3005, 3006, 3015				3005, 3006			3015
FS-MMTT	3002, 3005, 3015				3002, 3005			3015
Body weight	All	All	All	All	All but 3008	3009, 3015	3009, 3015	3009, 3015
Waist circumference	All but 3004 and 3008				All but 3004 and 3008			3009, 3015
Blood pressure	All	All	All	All	All but 3008	3009, 3015	3009, 3015	3009, 3015
DXA[c]	3009, 3010				3010			3009
CT scan (abdominal)	3009							3009

[a] Week 18 of double-blind treatment period was the prespecified efficacy endpoint for DIA3008 substudies. Subsequent assessments for DIA3008, therefore, are not shown on this table.
[b] FPG also measured at Week 3 in DIA3004 and Week 4 in DIA3009.
[c] Baseline DXA for assessment of body composition performed at start of run-in period in DIA3010.
Key: CT = computerized tomography, DXA = dual energy x-ray absorptiometry, FPG = fasting plasma glucose, FS-MMTT = frequently-sampled mixed-meal tolerance test, MMTT = mixed-meal tolerance test, Rand. = randomization, Wk = week.
Note: Clinic visits were Weeks 3, 6, 12, 18, 26, 34, 42, and 52 in DIA3004; Weeks 4, 8, 12, 18, 26, 36, 44, and 52 in DIA3009; and Weeks 6, 12, 18, 26, 34, 42, and 52 in DIA3015.
Source: ISE, Table 3

Throughout Phase 3 trials, all subjects were to have a follow-up telephone contact (or optional study visit) about 30 days after the last dose of study drug to collect any serious adverse events since the last visit. Also, subjects who discontinued the study drug before study completion were withdrawn from the trial, and subjects withdrawn early from the trial were contacted by telephone at which Week 26 and Week 52 visit would have occurred to collect any CV outcome events or adverse events of fracture.

Glycemic Rescue:

Subjects in Phase 3 trials were to remain on stable doses of background antidiabetic treatment at the beginning of the run-in period throughout the double-blind treatment period, except for persistent hyperglycemia, which led to subjects receiving rescue therapy or withdrawing from the trial. Criteria for rescue were based on repeated and confirmed (within 7 days) FPG values through Week 18 in DIA3008 sub-studies or Week 26 in all other Phase 3 trials, and on HbA1c values thereafter. Subjects receiving rescue therapy continued on double-blind study drug treatment and trial procedures related to the protocol until completion of trial. The glycemic thresholds for rescue were largely similar across all the Phase 3 trials; the specific rescue therapy for each trials are listed in Table 4 below. Of note, there was no rescue therapy for DIA3015; subjects who met prespecified glycemic levels in DIA3015 were withdrawn from the trial.

Table 4: Protocol Specified Rescue Therapy Across Phase 3 Trials

3002	Insulin
3004	No standard rescue therapy specified: rescue medications selected as clinically appropriate and may also include up-titration of current AHA medication(s)
3005	Metformin
3006	Glimepiride
3008	No standard rescue therapy specified: rescue medications selected as clinically appropriate
3009	Pioglitazone
3010	No standard rescue therapy specified; rescue selected as clinically appropriate.
3012	Glimepiride
3015	No rescue criteria used as withdrawal criteria

Source: ISE, section 12.1 of attachment 1.1

1.4 Baseline Demographics

The baseline demographic, anthropometric, and diabetic characteristics for each Phase 3 trial are summarized in Table 5, Table 6, and Table 7; the data shows the demographic characteristics combining all treatment groups within each trial. Baseline characteristics between treatment groups within each trial were balanced (data not shown).

The median age of subjects in most Phase 3 trials was 55 to 60 years of age, and was older in subjects in DIA3004 (Moderate Renal Impairment Study), DIA3008 (Cardiovascular Safety Study), and DIA3010 (Older Adults Study), which was anticipated based on the study entry criteria. Whites represented the most common racial group in all studies, with a small representation of African-American subjects. A large proportion of subjects were overweight and the majority of subjects were obese (baseline BMI ≥30 kg/m^2). There were slightly more obese subjects in the add-on to metformin and sulfonylurea trial (DIA3002) and in the add-on to basal insulin trial. The mean baseline HbA1c ranged from 7.7 to 8.4%. As anticipated, subjects in the monotherapy trial (DIA3005) had the shortest median diabetes duration (3 years) and subjects in DIA3004 and DIA3008 had the longest duration of diabetes (median 15 years) in the Phase 3 trials. Baseline estimated GFR (eGFR) was reflective of diabetes duration and subject

median age. The mean baseline eGFR was lower in DIA3004 and DIA3008 compared to the other Phase 3 trials as per entry criteria.

Table 5: Baseline Demographic Characteristics by Phase 3 Trial

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3009 Add-on to Metformin	DIA3008 SU Substudy[a]	DIA3002 Add-on to Metformin + SU	DIA3015 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + PIO	DIA3008 Substudy[b]	DIA3004 Renal Impairment	DIA3010 Older Adults
Age (years)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	55.4 (10.61)	55.4 (9.42)	56.2 (9.22)	64.8 (7.65)	56.7 (9.30)	56.7 (9.46)	57.4 (10.03)	62.8 (7.65)	68.5 (8.28)	63.6 (6.24)
Median	56.0	56.0	57.0	65.0	58.0	57.0	57.0	63.0	69.0	63.0
Range	(24;79)	(21;79)	(22;80)	(44;82)	(27;79)	(21;91)	(27;78)	(32;85)	(39;96)	(55;80)
Category, n (%)										
<35	21 (3.6)	19 (1.5)	20 (1.4)	0	6 (1.3)	10 (1.3)	2 (0.6)	1 (0.1)	0	0
35 – <65	445 (76.2)	1059 (82.5)	1187 (81.9)	58 (45.7)	379 (80.8)	601 (79.6)	247 (72.2)	1017(59.2)	83 (30.9)	441 (61.8)
≥65	118 (20.2)	206 (16.0)	243 (16.8)	69 (54.3)	84 (17.9)	144 (19.1)	93 (27.2)	700 (40.7)	186 (69.1)	273 (38.2)
Sex, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
Male	258 (44.2)	605 (47.1)	756 (52.1)	72 (56.7)	239 (51.0)	422 (55.9)	216 (63.2)	1143 (66.5)	163 (60.6)	396 (55.5)
Female	326 (55.8)	679 (52.9)	694 (47.9)	55 (43.3)	230 (49.0)	333 (44.1)	126 (36.8)	575 (33.5)	106 (39.4)	318 (44.5)
Race, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
White	395 (67.6)	901 (70.2)	978 (67.4)	95 (74.8)	387 (82.5)	485 (64.2)	252 (73.7)	1342 (78.1)	215 (79.9)	552 (77.3)
Black, African-American	41 (7.0)	45 (3.5)	61 (4.2)	1 (0.8)	26 (5.5)	88 (11.7)	20 (5.8)	45 (2.6)	5 (1.9)	57 (8.0)
Asian	85 (14.6)	182 (14.2)	284 (19.6)	29 (22.8)	4 (0.9)	132 (17.5)	55 (16.1)	230 (13.4)	27 (10.0)	61 (8.5)
Other[c]	63 (10.8)	156 (12.1)	127 (8.8)	2 (1.6)	52 (11.1)	50 (6.6)	15 (4.4)	101 (5.9)	22 (8.2)	44 (6.2)
Ethnicity, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
Hispanic or Latino	180 (30.8)	373 (29.0)	242 (16.7)	11 (8.7)	109 (23.2)	159 (21.1)	54 (15.8)	121 (7.0)	21 (7.8)	104 (14.6)
Not Hispanic or Latino	402 (68.8)	908 (70.7)	1202 (82.9)	116 (91.3)	359 (76.5)	594 (78.7)	283 (82.7)	1591 (92.6)	240 (89.2)	607 (85.0)
Unknown/Not reported	2 (0.3)	3 (0.3)	6 (0.4)	0	1 (0.2)	2 (0.2)	5 (1.5)	6 (0.4)	8 (3.0)	3 (0.4)

[a] Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification).
[b] Data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 IU/day).
[c] Includes racial categories of American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Other, and Not Reported.
Key: ISE = Integrated Summary of Efficacy, N(n) = number, PIO = pioglitazone, SD = standard deviation, SU = sulfonylurea.
Note: Percentages calculated with the number of subjects in each group as denominator.
Source: ISE, Table 20

Table 6: Baseline Anthropometric Characteristics by Phase 3 Trial

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3009 Add-on to Metformin	DIA3008 SU Substudy[a]	DIA3002 Add-on to Metformin + SU	DIA3015 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + PIO	DIA3008 Substudy[b]	DIA3004 Renal Impairment	DIA3010 Older Adults
Baseline weight (kg)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	86.8 (20.44)	87.2 (21.70)	86.6 (19.78)	83.0 (18.73)	92.8 (22.35)	88.3 (23.20)	94.1 (23.49)	97.0 (21.27)	91.2 (17.95)	89.5 (16.76)
Baseline BMI (kg/m^2)										
N	584	1283	1450	127	469	755	342	1715	269	714
Mean (SD)	31.6 (6.24)	31.8 (6.24)	31.0 (5.41)	29.9 (5.79)	33.0 (6.48)	31.6 (6.91)	32.6 (6.76)	33.8 (6.29)	33.0 (6.15)	31.6 (4.57)
Category, n (%)										
<30	266 (45.6)	565 (44.0)	673 (46.4)	72 (56.7)	159 (33.9)	355 (47.0)	133 (38.9)	491 (28.6)	87 (32.3)	270 (37.8)
≥30	318 (54.4)	718 (55.9)	777 (53.6)	55 (43.3)	310 (66.1)	400 (53.0)	209 (61.1)	1224 (71.2)	182 (67.7)	444 (62.2)

[a] Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification).
[b] Data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 IU/day).
Key: BMI = body mass index, ISE = Integrated Summary of Efficacy, N(n) = number, PIO = pioglitazone, SD = standard deviation, SU = sulfonylurea..
Note: Percentages calculated with the number of subjects in each group as denominator.
Source: ISE, Table 21

Table 7: Baseline Diabetes Characteristics by Phase 3 Trial

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3009 Add-on to Metformin	DIA3008 SU Substudy[a]	DIA3002 Add-on to Metformin + SU	DIA3015 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + PIO	DIA3008 Substudy[b]	DIA3004 Renal Impairment	DIA3010 Older Adults
Baseline HbA_{1c} (%)										
N	584	1283	1450	127	469	755	342	1716	269	714
Mean (SD)	8.0 (0.97)	7.9 (0.90)	7.8 (0.79)	8.4 (1.00)	8.1 (0.92)	8.1 (0.91)	7.9 (0.96)	8.3 (0.90)	8.0 (0.87)	7.7 (0.78)
Category, n (%)										
<7.0%	68 (11.6)	161 (12.5)	195 (13.4)	3 (2.4)	33 (7.0)	64 (8.5)	43 (12.6)	59 (3.4)	29 (10.8)	108 (15.1)
7 - <8%	242 (41.4)	536 (41.7)	683 (47.1)	53 (41.7)	193 (41.2)	295 (39.1)	148 (43.3)	629 (36.6)	110 (40.9)	350 (49.0)
8 - <9%	177 (30.3)	402 (31.3)	441 (30.4)	33 (26.0)	152 (32.4)	247 (32.7)	91 (26.6)	642 (37.4)	94 (34.9)	202 (28.3)
9 - ≤10%	80 (13.7)	161 (12.5)	125 (8.6)	28 (22.0)	78 (16.6)	133 (17.6)	52 (15.2)	318 (18.5)	36 (13.4)[c]	53 (7.4)
>10%	17 (2.9)	23 (1.8)	6 (0.4)	10 (7.9)	13 (2.8)	16 (2.1)	8 (2.3)	68 (4.0)		1 (0.1)
Baseline FPG (mmol/L)										
N	583	1282	1450	126	469	755	342	1713	268	714
Mean (SD)	9.5 (2.31)	9.4 (2.32)	9.2 (2.06)	10.0 (2.55)	9.5 (2.20)	9.3 (2.56)	9.2 (2.22)	9.4 (2.78)	9.1 (2.75)	8.7 (2.12)
Duration of diabetes (years)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	4.3 (4.40)	6.9 (5.35)	6.6 (5.33)	10.2 (6.37)	9.6 (6.26)	9.6 (6.16)	10.6 (7.00)	16.6 (7.49)	16.3 (8.52)	11.7 (7.45)
Median	3.0	5.7	5.0	9.0	8.6	8.0	9.7	15.0	15.0	10.0
Baseline eGFR- (mL/min/1.73m²)										
N	584	1284	1449	125	469	755	342	1716	269	714
Mean (SD)	87.1 (20.28)	88.6 (18.47)	90.2 (18.74)	69.3 (18.55)	89.4 (19.65)	87.5 (19.14)	86.4 (18.59)	74.9 (19.02)	39.4 (6.88)	77.5 (16.57)
Median	85.0	87.0	88.2	69.0	88.0	86.0	84.0	74.0	39.0	76.0
Range	(38,227)	(44,169)	(33,181)	(32,116)	(26,163)	(50.0;164.0)	(48,144)	(27,159)	(24,61)	(37,153)
Category, n (%)										
<60	32 (5.5)	40 (3.1)	38 (2.6)	44 (35.2)	15 (3.2)	41 (5.4)	25 (7.3)	348 (20.3)	268 (99.6)	94 (13.2)
60 - <90	324 (55.5)	665 (51.8)	715 (49.3)	65 (51.2)	235 (50.1)	382 (50.6)	184 (53.8)	1014 (59.0)	1 (0.4)	456 (63.9)
≥90	228 (39.0)	579 (45.1)	696 (48.0)	16 (12.6)	219 (46.7)	332 (44.0)	133 (38.9)	354 (20.6)		164 (23.0)
Subjects with microvascular complications										
N	584	1284	1450	127	469	755	342	1718	269	714
n (%)	40 (6.8)	286 (22.3)	269 (18,6)	55 (43.3)	124 (26.4)	251 (33.2)	66 (19.3)	1026 (59.7)	216 (80.3)	212 (29.7)
Baseline SBP (mmHg)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	127.7 (12.95)	128.2 (12.99)	129.8 (13.22)	136.2 (12.93)	130.5 (13.52)	130.7 (13.57)	127.2 (12.21)	137.8 (16.65)	134.9 (14.01)	131.1 (13.32)
Baseline TG (mmol/L)										
N	584	1284	1449	127	469	755	342	1715	269	714
Mean (SD)	2.09 (1.236)	2.09 (1.395)	2.05 (1.611)	2.00 (1.061)	2.22 (1.471)	1.98 (1.347)	1.64 (1.064)	1.96 (1.421)	1.98 (1.049)	1.76 (1.148)

a Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification).
b Data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 IU/day).
c For DIA3004, this baseline HbA_{1c} category was 9 to ≤10.5%.
Key: AHA = antihyperglycemic agent, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL-C = high density lipoprotein-cholesterol, ISE = Integrated Summary of Efficacy, N(n) = number, PIO = pioglitazone, SBP = systolic blood pressure, SD = standard deviation, TG = triglycerides, trt = treatment.
Note: Percentages calculated with the number of subjects in each group as denominator.
Source: ISE, Table 22

2 Efficacy

2.1 Analysis Datasets

The primary analysis set for efficacy was the modified intent-to-treat (mITT) analysis set, which included all randomized subjects who took at least one dose of double-blind study drug. For efficacy, missing data was imputed using the last observation carried forward (LOCF) method. For a given efficacy variable, only those subjects with both baseline and at least one post-baseline measure were included. Baseline was the pre-dose measure at Day 1.

In addition to evaluating glycemic efficacy in each Phase 3 trials, a pooled population of subjects with baseline eGFR of ≥30 to <60 mL/min/1.73m² from Phase 3 trials was used to evaluate glycemic response in subjects with moderate renal impairment. Most Phase 3 trials only included subjects with eGFR of ≥55 mL/min/1.73m² except for DIA3004 (eGFR of ≥30 to <50

mL/min/1.73m^2) and DIA3008 (eGFR of ≥30 mL/min/1.73m^2). Subjects with eGFR ≥50 mL/min/1.73m^2 were eligible for trial in DIS3005 and DIA3010.

2.2 Subject Disposition and Exposure

Across the Phase 3 clinical trials, a total of 7803 subjects were randomized and received at least one dose of study drug (mITT analysis set). This number includes only those subjects from trial DIA3008 who participated in the insulin and sulfonylurea sub-studies. Of 7803 subjects receiving study drug, 4994 subjects were treated with canagliflozin (2302 subjects with 100 mg and 2692 subjects with 300 mg), 1583 subjects were treated with placebo, and 1226 subjects were treated with active comparator (744 with sitagliptin and 482 with glimepiride). Table 8 presents mITT population for each Phase 3 trial.

Table 8: Subjects in Modified Intent-to-Treat (mITT) Analysis Set by Phase 3 Trial

Study Type/ Study ID	Number of Subjects in mITT Analysis Set					
	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride	Overall Total
Monotherapy						
DIA3005 - Main Study	192	195	197			584
DIA3005 – High Glycemic substudy		47	44			91
Dual therapy						
DIA3006 –Add-on to metformin	183	368	367	366		1284
DIA 3009 – Add-on to metformin		483	485		482	1450
DIA3008 substudy – Add-on to SU[a]	45	42	40			127
Triple therapy						
DIA3002 – Add-on to metformin & SU	156	157	156			469
DIA3012 – Add-on to metformin & PIO	115	113	114			342
DIA3015 – Add-on to metformin & SU			377	378		755
Add-on to insulin						
DIA3008 substudy[b]	565	566	587			1718
Special populations						
DIA3004 - moderate renal impairment	90	90	89			269
DIA3010 - older adults	237	241	236			714
Total subjects	**1583**	**2302**	**2692**	**744**	**482**	**7803**

[a] Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification).

[b] Data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 IU/day).

Key: CANA = canagliflozin, mITT = modified Intent-to-Treat, PIO = pioglitazone, SU = sulfonylurea.

Source: ISE, Table 18

The overall mean duration of subject exposure before rescue was slightly greater in the canagliflozin groups compared to placebo for each Phase 3 trials, as shown in Table 9, except for DIA3008 SU substudy.

Table 9: Duration of Exposure to Study Drug Prior to Rescue by Phase 3 Trial (mITT)

Study Type/ Study ID	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Monotherapy					
DIA3005 - Main Study					
N	192	195	197		
Total duration, mean (SD)	21.51 (7.311)	24.03 (6.363)	24.21 (5.639)		
DIA3005 – High Glycemic substudy					
N		47	44		
Total duration, mean (SD)		23.39 (7.129)	23.52 (7.602)		
Dual therapy					
DIA3006 –Add-on to metformin					
N	183	368	367	366	
Total duration, mean (SD)	22.44 (6.921)	24.07 (5.751)	24.52 (5.304)	23.99 (5.416)	
DIA 3009 – Add-on to metformin					
N		483	485		482
Total duration, mean (SD)		46.10 (13.241)	44.98 (14.653)		44.71 (14.124)
DIA3008 substudy – Add-on to SU[a]					
N	45	42	40		
Total duration, mean (SD)	16.58 (4.176)	16.98 (3.930)	17.62 (3.285)		
Triple therapy					
DIA3002 – Add-on to metformin and SU					
N	156	157	156		
Total duration, mean (SD)	22.22 (6.938)	23.69 (5.882)	23.64 (6.056)		
DIA3012 – Add-on to metformin and PIO					
N	115	113	114		
Total duration, mean (SD)	22.55 (6.099)	24.68 (5.008)	24.14 (5.577)		
DIA3015 – Add-on to metformin and SU					
N			377	378	
Total duration, mean (SD)			42.64 (15.641)	41.44 (14.861)	
Add-on to insulin					
DIA3008 substudy[b]					
N	565	566	587		
Total duration, mean (SD)	16.59 (4.067)	17.32 (3.149)	17.15 (3.628)		
Special populations					
DIA3004 - moderate renal impairment					
N	90	90	89		
Total duration, mean (SD)	22.34 (7.375)	22.76 (7.017)	24.61 (4.694)		
DIA3010 - older adults					
N	237	241	236		
Total duration, mean (SD)	22.69 (6.877)	24.93 (4.586)	24.37 (5.371)		

[a] Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification).

[b] Data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 IU/day).

Key: CANA = canagliflozin, ISE = Integrated Summary of Efficacy, N = number, PIO = pioglitazone, SD = standard deviation, SU = sulfonylurea.

Note: Total duration = Treatment duration = last dose date - first dose date + 1(in days).

Note: Duration summarized up through primary assessment timepoint: Week 18 (DIA3008 SU and Insulin substudies), Week 26 (DIA3005, DIA3006, DIA3002, DIA3012), and Week 52 (DIA3009, DIA3015).

Source: ISE, Table 19

The completion rates for canagliflozin treatment groups for trials with a primary endpoint at Week 26 ranged from 80 to 90% in DIA3005, DIA3006, DIA3002, DIA3012, DIA3004, and DIA3010, which was higher than the corresponding completion rates in the placebo group (62 to 72%). The lower completion rates with placebo may be attributable to lack of efficacy, as reflected by a higher proportion of subjects on placebo receiving glycemic rescue compared to canagliflozin, which would not be unexpected. The completion rates for trials with primary assessment at Week 52 was lower and ranged from 67 to 74% with canagliflozin for DIA3009 and DIA3015; the completion rate was higher with canagliflozin compared to the comparator (glimepiride and sitagliptin). In DIA3015, rescue therapy was not allowed and subjects who met

pre-specified glycemic levels were withdrawn from the trial, which may have contributed to the lower completion rate in DIA3015 compared to other Phase 3 trial.

Table 10: Subject Disposition (N[%]) of All Randomized Subjects in Phase 3 Trials

	Placebo	Cana 100	Cana 300	Sitagliptin	Glimepiride
Monotherapy					
DIA3005	194	196	197		
Completed	121 (62)	168 (86)	171 (87)		
Discontinued due to adverse event	2 (1)	5 (3)	3 (2)		
Rescued	44 (23)	5 (3)	4 (2)		
Dual therapy					
DIA3006 - add-on to metformin	183	368	367	366	
Completed	130 (71)	317 (86)	322 (88)	299 (82)	
Discontinued due to adverse event	7 (4)	18 (5)	6 (2)	8 (2)	
Rescued	27 (15)	6 (2)	1 (<1)	23 (6)	
DIA3009 - add-on to metformin		483	485		484
Completed		365 (76)	357 (74)		337 (70)
Discontinued due to adverse event		25 (5)	33 (7)		26 (5)
Rescued		32 (7)	24 (5)		51 (11)
DIA3008 SU substudy - add-on to SU*	45	42	40		
Completed	34 (76)	37 (88)	38 (95)		
Discontinued due to adverse event	0	0	1 (3)		
Rescued	8 (18)	2 (5)	0		
Triple Therapy					
DIA3002 - add-on to metformin & SU	156	157	156		
Completed	107 (69)	127 (81)	126 (81)		
Discontinued due to adverse event	6 (4)	8 (5)	8 (5)		
Rescued	20 (13)	2 (1)	3 (2)		
DIA3012 - add-on to metformin & pio	115	115	114		
Completed	79 (69)	103 (90)	101 (89)		
Discontinued due to adverse event	24 (21)	9 (8)	13 (11)		
Rescued	14 (12)	1 (1)	0		
DIA3015 - add-on to metformin & SU			378	378	
Completed			254 (67)	210 (56)	
Discontinued due to adverse event			21 (6)	14 (4)	
Add-on to insulin					
DIA3008 insulin substudy	565	566	587		
Completed	465 (82)	506 (89)	520 (89)		
Discontinued due to adverse event	9 (2)	9 (3)	23 (4)		
Rescued	49 (9)	23 (4)	18 (3)		
Special Population					
DIA3004 - moderate renal impairment	91	90	91		
Completed	65 (71)	72 (80)	79 (87)		
Discontinued due to adverse event	4 (4.4)	4 (4.4)	2 (2.2)		
Rescued	13 (14.3)	4 (4.4)	3 (3.3)		
DIA3010 - older adults	239	241	236		
Completed	172 (72)	221 (92)	208 (88)		
Discontinued due to adverse event	8 (3.4)	4 (1.7)	10 (4.2)		
Rescued	26 (10.9)	5 (2.1)	1 (0.4)		

*Population 1

Source: Tables 2 and 3 from CSR for each individual trial

2.3 Primary Endpoint

Please refer to Dr. Wei Liu's review for full discussion of efficacy. I will only briefly summarize the primary efficacy results observed in each Phase 3 trial here.

Table 11 presents the placebo-subtracted least squares (LS) mean change in HbA1c from baseline for all placebo-controlled Phase 3 trial. The placebo-adjusted mean reductions in HbA1c was dose-dependent and consistently significant, and ranged from 0.3 to 0.9% with canagliflozin 100 mg and 0.4 to 1.2% with canagliflozin 300 mg. Not surprisingly, modest efficacy was observed in DIA3004, which included subjects with moderate renal impairment with baseline eGFR of ≥30 to <50 mL/min/1.73m^2. As discussed in section 2.1, the efficacy results of canagliflozin in a pooled dataset with moderate renal impairment with eGFR criteria of ≥30 to <60 mL/min/1.73m^2 was evaluated and is discussed further in section 2.3.

Table 11: Placebo-subtracted LS Mean HbA1c Change from Baseline (95 CI) to Primary Assessment Timepoint in Phase 3 Trial (LOCF, mITT)

	Cana 100 mg	Cana 300 mg
DIA3005 - Monotherapy	-0.9 (-1.1;-0.7)	-1.2 (-1.3;-1.0)
DIA3006 - Add-on to metformin	-0.6 (-0.7;-0.5)	-0.8 (-0.9;-0.6)
DIA3008 - Add-on to SU substudy	-0.7 (-1.1;-0.3)	-0.8 (-1.2;-0.4)
DIA3002 - Add-on to metformin+SU	-0.7 (-0.9;-0.5)	-0.9 (-1.1;-0.7)
DIA3012 - Add-on to metformin+pio	-0.6 (-0.8;-0.4)	-0.8 (-1.0;-0.6)
DIA3008 - Add-on to insulin substudy	-0.7 (-0.7;-0.6)	-0.7 (-0.8;-0.6)
DIA3004- Moderate renal impairment	-0.3 (-0.5;-0.1)	-0.4 (-0.6;-0.2)
DIA3010 - Older adults	-0.6 (-0.7;-0.4)	-0.7 (-0.8;-0.6)

Source: ISE, Table 23

In the active-comparator (glimepiride) trial DIA3009 (add-on to metformin), the LS mean change in HbA1c from baseline at Week 52 was -0.8 and -0.9% with canagliflozin 100 mg and 300 mg respectively compared to -0.8% with glimepiride. The observed treatment difference was -0.01 for canagliflozin 100 mg (95% CI:-0.11;0.09) and -0.12% for canagliflozin 300 mg (95% CI:-0.22;-0.02) when compared to glimepiride.

In the active-comparator (sitagliptin) trial of DIA3015 (add-on to metformin and SU) which only studied canagliflozin 300 mg dose, the LS mean change in HbA1c from baseline at Week 52 was -1.0% with canagliflozin 300 mg and -0.7% with sitagliptin. The observed treatment difference was -0.4 for canagliflozin 300 mg (95% CI:-0.5;-0.25) when compared to sitagliptin.

In both active-controlled non-inferiority trial, the non-inferiority (NI) margin was 0.3% and the upper limits of both 95% CIs for between-group difference were below the NI margin in all canagliflozin groups, meeting the pre-specified criteria of non-inferiority.

2.4 Efficacy in Renal Impairment

As shown in Table 11, the glycemic efficacy was modest in DIA3004 (moderate renal impairment) compared to other Phase 3 trials which enrolled a population of subjects with normal to mild renal function. In order to evaluate the efficacy of canagliflozin in subjects with moderate renal impairment, the glycemic efficacy was further evaluated in a pooled dataset of subjects with baseline eGFR of ≥30 to <60 mL/min/1.73m^2. The Phase 3 trials that allowed enrollment of subjects within this eGFR were DIA3004, DIA3005, DIA3008, and DIA3010, and the subjects from each trial contributing to this pooled dataset are detailed in Table 12. DIA3008 contributed the largest number of subjects.

Table 12: Subjects in the Pooled Dataset for Moderate Renal Function (mITT)

Study Type/ Study ID	Timing of Primary Endpoint	Number of Subjects Contributing Data to Pooled Population			
		Placebo	CANA 100 mg	CANA 300 mg	Total
Monotherapy					
DIA3005 – main study	26 weeks	10	10	12	32
Add-on to existing AHA therapy					
DIA3008 - entire study	18 weeks	252	208	246	706
Special populations					
DIA3004 – renal impairment	26 weeks	85	87	81	253
DIA3010 – older adults	26 weeks	35	33	26	94
Overall total		**382**	**338**	**365**	**1085**

Key: AHA = antihyperglycemic agent, CANA = canagliflozin.

Source: ISE, Table 70

In this pooled moderate renal impairment population, more subjects in the canagliflozin group (86-87%) compared to placebo (62%) completed the double-blind period through the primary assessment timepoint (Table 13).

Table 13: Subject Disposition in the Pooled Dataset for Moderate Renal Function (All Randomized)

	Placebo	Cana 100	Cana 300
N	383	339	366
Completed	121 (62)	168 (86)	171 (87)
Discontinued due to adverse event	14 (4)	10 (3)	15 (4)
Rescued	48 (13)	19 (6)	13 (4)

Source: ISS, Table 71, DSUB03E_RF

Table 14 presents the results of HbA1c change from baseline in this pooled dataset of subjects with moderate renal function. The placebo-subtracted LS mean reduction in HbA1c was higher than what was observed in DIA3004 at 0.4 and 0.5% with canagliflozin 100 mg and 300 mg. This is most likely due to the fact that the average renal function, as measured by eGFR, was better in this pooled population compared to DIA3004; the mean eGFR was 40 mL/min/1.73m^2 in DIA3004 compared to 48 mL/min/1.73m^2 in this pooled dataset of subjects with moderate renal impairment.

A subgroup analysis of change in HbA1c by baseline eGFR, as shown in Table 14, show that the glycemic efficacy becomes modest in the subgroup of subjects at the lower half of moderate renal function (<45 mL/min/1.73m^2), further demonstrating that the efficacy decreases with progressive decline in renal funciton. As a result, although the treatment difference showed statistical significance, the glycemic efficacy with 100 mg dose of canagliflozin was significantly reduced in those with baseline eGFR <45 mL/min/1.73m^2 with 0.2% placebo-subtracted LS mean reduction in HbA1c.

Table 14: LS Mean Change in HbA1c (%) from Baseline to Primary Assessment Timepoint in Pooled Subjects with Moderate Renal Function (LOCF; mITT)

	Placebo	Cana 100 mg	Cana 300 mg
N	382	338	365
LS mean (SE) change from baseline	-0.1 (0.1)	-0.5 (0.1)	-0.6 (0.1)
Difference of LS mean (SE) (95% CI)		-0.4 (0.1) (-0.5;-0.3)	-0.5 (0.1) (-0.6;-0.4)
By eGFR Category			
Baseline eGFR <45 mL/min/1.73m^2, n	108	118	122
LS mean (SE) change from baseline	0.1 (0.2)	-0.2 (0.2)	-0.3 (0.2)
Difference of LS mean (SE) (95% CI)		-0.2 (0.1) (-0.5;-0.0)	-0.4 (0.1) (-0.6;-0.2)
Baseline eGFR ≥45 mL/min/1.73m^2, n	248	208	232
LS mean (SE) change from baseline	-0.1 (0.1)	-0.6 (0.1)	-0.6 (-0.1)
Difference of LS mean (SE) (95% CI)		-0.5 (-.1) (-0.6;-0.3)	-0.5 (0.1) (-0.7;-0.4)

Source: ISE, Table 75, 76

2.5 Other Endpoints - Blood Pressure, Body Weight, and Lipid Changes

The pre-specified secondary efficacy endpoints in Phase 3 trials that were not related to glycemic control included changes in systolic blood pressure, the percent change in body weight, fasting triglycerides, and HDL-C. The placebo-subtracted LS mean change in systolic blood pressure and percent change in body weight is presented in Table 15, and the change in fasting HDL-C and triglycerides are presented in Table 16. Similar to the primary efficacy endpoint, the these endpoints were measured at Week 18 for DIA3008 SU and insulin sub-studies and Week 26 for all other trials.

As shown in Table 15, there was a dose-dependent and significant placebo-subtracted LS mean reduction in systolic blood pressure (SBP) from baseline to the primary assessment timepoint, except for trials where canagliflozin was studied as an add to SU (DIS3002 and DIA3008 SU substudy) where the changes in blood pressure did not reach statistical significance with both doses of canagliflozin. In the remaining placebo-controlled trials, the placebo-subtracted LS mean reduction in SBP ranged from 2.6 to 5.7 mmHg and 3.5 to 7.9 mmHg with 100 mg and 300 mg respectively.

There was a dose-dependent and significant placebo-subtracted LS mean percent reduction in the body weight from baseline to the primary assessment timepoint, except with the 100 mg dose of canagliflozin in DIA3008 SU substudy where it did not reach statistical significance. Similar to changes in SBP, although the change in percent body weight in the 300 mg dose of canagliflozin

in DIA3008 SU substudy and DIA3002 were statistically significant, these changes were modest compared to the other Phase 3 trials where SU was not a background AHA therapy. The placebo-subtracted LS mean reduction of percent body weight in the remaining trials where SU was not a background therapy ranged from 1.6 to 2.4% with 100 mg and 1.8 to 3.8% with 300 mg dose.

Table 15: Placebo-Subtracted LS Mean Change of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and % Body Weight from Baseline (95% CI) to Primary Assessment Timepoint in Placebo-Controlled Phase 3 Trial - LOCF, mITT

Trial	SBP (mmHg)		% Body Weight	
	Cana 100	Cana 300	Cana 100	Cana 300
DIA3005 - Monotherapy	-3.7 (-5.9;-1.6)	-5.4 (-7.6;-3.3)	-2.2 (-2.9;-1.6)	-3.3 (-4.0;-2.6)
DIA3006 - Add-on to metformin	-5.4 (-7.3;-3.4)	-6.6 (-8.5;-4.7)	-2.5 (-3.1;-1.9)	-2.9 (-3.5;-2.3)
DIA3008 - Add-on to SU substudy	-0.1 (-6.5;6.2)	-1.8 (-8.2;4.7)	-0.4 (-1.8;1.0)	-1.8 (-3.2;-0.4)
DIA3002 - Add-on to metformin+SU	-2.2 (-4.7;0.2)	-1.6 (-4.1;0.9)	-1.4 (-2.1;-0.7)	-2.0 (-2.7;-1.3)
DIA3012 - Add-on to metformin+pio	-4.1 (-6.9;-1.3)	-3.5 (-6.3;-0.6)	-2.7 (-3.6;-1.8)	-3.7 (-4.6;-2.8)
DIA3008 - Add-on to insulin substudy	-2.6 (-4.1;-1.1)	-4.4 (-5.9;-2.9)	-1.9 (-2.2;-1.6)	-2.4 (-2.7;-2.1)
DIA3004- Moderate renal impairment	-5.7 (-9.5;-1.9)	-6.1 (-10.0;-2.3)	-1.6 (-2.3;-0.8)	-1.8 (-2.6;-1.0)
DIA3010 - Older adults	-4.6 (-6.8;-2.4)	-7.9 (-10.1;-5.6)	-2.3 (-2.8;-1.7)	-3.0 (-3.5;-2.4)

Source: ISE, Tables 29, 34

As shown in Table 16, the increase in HDL-C with canagliflozin was statistically significant in four of eight placebo-controlled Phase 3 trials. The decrease in triglycerides with canagliflozin was small and reached statistically significant in only one of eight placebo-controlled trials (DIA3012). During the clinical development of canagliflozin, an increase in LDL-C levels was noted, which is further discussed in section 3.12 under Safety.

Table 16: Placebo-Subtracted LS Mean Percent Change of HDL-C and Triglycerides from Baseline to Primary Assessment Timepoint in Placebo-Controlled Phase 3 Trials - LOCF, mITT

Trial	HDL-C (mg/dL)		Triglycerides (mg/dL)	
	Cana 100	Cana 300	Cana 100	Cana 300
DIA3005 - Monotherapy	6.7 (2.9;10.6)	6.0 (2.2;9.9)	-5.3 (-14.8;4.1)	-10.2 (-19.6;-0.8)
DIA3006 - Add-on to metformin	6.7 (3.6;9.7)	8.5 (5.4;11.5)	-1.6 (-9.9;6.7)	-4.7 (-13.0;3.7)
DIA3008 - Add-on to SU substudy	2.5 (-5.5;10.5)	0.8 (-7.2;8.8)	-12.9 (-28.4;2.7)	12.2 (-2.9;27.3)
DIA3002 - Add-on to metformin+SU	2.5 (-0.9;5.9)	3.4 (-0.1;6.8)	-6.2 (16.9;4.5)	-3.1 (-13.8;7.6)
DIA3012 - Add-on to metformin+pio	4.8 (1.2;8.5:	6.5 (2.8;10.2)	-12.1 (-23.3;-0.9)	-16.9 (-28.1;-5.8)
DIA3008 - Add-on to insulin substudy	0.9 (-1.3;3.0)	4.7 (2.5;6.9)	0.2 (-4.9;5.3)	-2.0 (-7.0;3.0)
DIA3004- Moderate renal impairment	2.6 (-1.9;7.0)	1.4 (-3.0;5.8)	-1.7 (-13.9;10.4)	4.0 (-8.1;16.0)
DIA3010 - Older adults	5.3 (2.6;7.9)	4.7 (2.0;7.4)	-4.8 (-12.1;2.5)	0.7 (-6.6;8.1)

Source: ISS, DEFF08X_SS, DEFF10X_SS

3 Safety

3.1 Analysis Datasets

Four pooled datasets of Phase 3 trials were used to evaluate the safety of canagliflozin, as shown in Table 17. It should be noted that one of nine Phase 3 trial, DIA3015, was not included in any of the pooled dataset because it was an active-controlled (sitagliptin) trial which included only one of two active canagliflozin groups (300 mg group only).

All safety analyses were based on the safety analysis set, which included all randomized subjects who received at least one dose of study drug. Treatment-emergent adverse events (TEAE) were analyzed, which was defined as an adverse event with an onset after initiation of double-blind study drug, or within 30 days of the last intake of study drug. Existing events before initiation of double-blind study drug were also considered TEAE if it increased in severity after initiation of study drug, or if the post-randomization change was considered related to the study drug by the investigator. For certain selected adverse events (e.g., fractures and malignancies), all events post-randomization were analyzed.

For laboratory data, all data regardless of rescue were used. Mean and median changes over time were presented for DS1 over 26 weeks, since trial visits and time and event scheduled differed across trials that comprise DS2 and DS3, making it difficult to estimate change over time consistently in the whole pooled population. The incidence of subjects with laboratory values meeting PDLC criteria assessment were evaluated in DS1, DS2, and DS3.

For adjudicated events such as malignancies, fractures, cardiovascular, thromboembolic, renal, and hepatic safety events, all events throughout clinical program (Phase 1 through 3) were reviewed.

Table 17: Pooled Datasets for Phase 3 Trials

Dataset Name	Dataset Description	Pooled Trials	Pooled Treatment Groups	Duration
Placebo-Controlled Studies Dataset (DS1)	All Placebo-controlled trials	DIA3002, DIA3005[1], DIA3006[2], DIA3012	Placebo Cana 100 mg Cana 300 mg All Cana	26 weeks
Moderate Renal Impairment Dataset (DS2)	Subjects with baseline eGFR ≥30 to <60 mL/min/1.73m^2	DIA3004 and subgroups from DIA3005[1], DIA3008, DIA3010	Placebo Cana 100 mg Cana 300 mg All Cana	26 weeks for all studies other than DIA3008 (through September 15, 2011)
Broad Dataset (DS3)	All Active- and Placebo-controlled trials[3]	DIA3002, DIA3004 DIA3005[1], DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	All Non-Cana (placebo, sitagliptin, or glimepiride) Cana 100 Cana 300 All Cana	26 weeks for all studies other than DIA3009 (52 weeks) and DIA3008 (through September 15, 2011)
Longer-term Exposure Broad Dataset (DS4)	All Active- and Placebo-controlled trials[3]	DIA3002, DIA3004 DIA3005[1], DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	All Non-Cana (placebo, sitagliptin, or glimepiride) Cana 100 Cana 300 All Cana	Data collected through January 31, 2012

Source: ISS, Table 3; Cana=canagliflozin
[1]High glycemic substudy is excluded.
[2]Sitagliptin treatment group is excluded.
[3]DIA3015 excluded.

The primary pooled population for safety evaluation was the 26-week Placebo-controlled Studies Dataset (DS1) since it included placebo-controlled trials with similar design over a common duration of treatment. However, given the exposure in this dataset is limited, larger pooled dataset (DS3) was used to provide additional safety assessments for adverse events with low incidence (i.e., hepatic events, malignancies, fractures). About 56% of population in DS3 are from DIA3010, DIA3004, and DIA3008, and as previously discussed, these subjects tended to be older with longer duration of diabetes, higher prevalence of diabetic comorbidities and complications in comparison to DS1.

The major difference between DS3 and DS4 is that while DS3 includes data through the protocol-specified primary evaluation time point (at Week 26 or Week 52) for all trials except for DIA3008 (data cutoff date of September 15, 2011), DS4 includes data beyond the primary evaluation time point through the end of January 2012. As a result, DS4 provide 50% additional

subject-years exposure compared to DS3 for evaluation of safety. The applicant points out that because many studies are still ongoing, data in DS4 are preliminary and not final.

A Moderate Renal Impairment Dataset (DS2) was used to assess the safety in subjects with moderate renal function (baseline eGFR ≥30 to <60 mL/min/1.73m^2). As discussed in efficacy dataset, this dataset mainly included subjects from DIA3004, DIA3005, DIA3008, and DIA3010.

The 4-month Safety Update included update of safety data with cutoff date of July 1, 2012. In addition, for malignancies, we requested an additional update, and the applicant provided an updated data with all cases of malignancies received as of November 15, 2012.

3.2 Exposure in Pooled Datasets for Safety

At the time of NDA submission, a total of 6645 subjects were exposed to canagliflozin in Phase 3 program. Of these, 5936 subjects were exposed for at least 6 months, 4723 subjects for at least 12 months, and 1200 subjects for at least 18 months. Table 18 displays the overall exposure by treatment arm.

Table 18: Overall Exposure in Canagliflozin Phase 3 Program: Safety Analysis Set

	Non-Cana	Cana 100 mg	Cana 300 mg	Cana Total
Total Number of Subjects	3640	3139	3506	6645
6-month Exposure	3162	2844	3092	5936
12-month Exposure	2392	2260	2463	4723
18-month Exposure	569	604	596	1200
24-month Exposure	64	73	71	144

Source: ISS, Table 15

Table 19 presents the exposure data for each pooled safety dataset described in section 3.1. The mean duration of exposure to canagliflozin was 24 weeks in the Placebo-Controlled Studies Dataset (DS1), and 88% of subjects were exposed to canagliflozin for at least 24 weeks. The mean duration of exposure to canagliflozin was substantially longer in the Broad Dataset (DS3) and Longer-term Exposure Broad Dataset (DS4) at 38 and 56 weeks respectively. About 30% and 72% of subjects were exposed to canagliflozin for at least 50 weeks in DS3 and DS4 respectively.

Table 19: Duration of Exposure to Study Drug for Each Pooled Dataset - Regardless of Rescue: Safety Analysis Set

DS1	Placebo	Cana 100	Cana 300 mg	Cana Total
N	646	833	834	1667
≥24 weeks	537 (83%)	728 (87%)	733 (88%)	1461 (88%)
Mean (SD)	24 (5.9)	24 (5.7)	24 (5.5)	24 (5.6)
Median	26	26	26	26
Total Exposure (subject years)	294.3	386.7	388.3	775
DS3	Non-Cana	Cana 100	Cana 300	Cana Total
N	3262	3092	3085	6177
≥50 weeks	897 (28%)	936 (30%)	896 (29%)	1832 (30%)
≥76 weeks	79 (2%)	93 (3%)	88 (3%)	181 (3%)
Mean (SD)	36 (17.4)	38 (17.4)	37 (17.8)	38 (17.6)
Median	30	32	31	32
Total Exposure (subject years)	2273.1	2260.6	2205.5	4466.1
DS4	Non-Cana	Cana 100	Cana 300	Cana Total
N	3262	3092	3085	6177
≥50 weeks	2182 (67%)	2260 (73%)	2211 (72%)	4471 (72%)
≥76 weeks	569 (17%)	605 (20%)	596 (19%)	1201 (19%)
Mean (SD)	54 (23.2)	57 (22.4)	56 (23.2)	56 (22.8)
Median	52	53	53	53
Total Exposure (subject years)	3379.5	3381.4	3306.3	6687.7
DS2	Placebo	Cana 100	Cana 300	Cana Total
N	382	338	365	703
≥50 weeks	75 (20%)	78 (23%)	87 (24%)	165 (24%)
≥76 weeks	12 (3%)	13 (4%)	8 (2%)	21 (3%)
Mean (SD)	36 (17.6)	37 (18.4)	37 (18.3)	37 (18.4)
Median	31	31	32	31
Total Exposure (subject years)	260.4	242.3	261.0	503.3

Source: ISS, Table 18, 20, 21, 23

The exposure data for DIA3008, which contributed the largest exposure data in the canagliflozin development program, are presented in Table 20 below. About 37% of subjects had at least 50 weeks of exposure to canagliflozin.

Table 20: Trial DIA3008 - Duration of Exposure to Study Drug: Safety Analysis Set

	Placebo	Cana 100	Cana 300	Cana Total
N	1441	1445	1441	2886
<6 weeks	41 (3%)	29 (2%)	55 (4%)	84 (3%)
6 to <24 weeks	110 (8%)	77 (5%)	93 (6%)	170 (6%)
24 to <50 weeks	780 (54%)	797 (55%)	778 (54%)	1575 (55%)
50 to <78 weeks	448 (31%)	468 (32%)	445 (31%)	913 (32%)
78 to <104 weeks	62 (4%)	74 (5%)	70 (5%)	144 (5%)
Mean (SD)	45 (18.7)	46 (18.0)	45 (19.1)	46 (18.5)
Median	44	44	43	44
Total Exposure (subject years)	1233.5	1284.4	1242.3	2526.7

Source: SCS, Table 18

At the time of 4-Month Safety Update (data cutoff date of July 1, 2012), the total exposure to canagliflozin was 8603 subject-years, which represented about 20% increase in the total exposure of subjects to canagliflozin compared to DS4.

3.3 Malignancies

In the long-term carcinogenicity study in rats, orally administered canagliflozin caused an increase in Leydig cell tumors (LCT) at all doses, in renal tubular tumors (RTT) and in the numbers of pheochromocytomas in both gender at the highest dose studied (100 mg/kg/day). The applicant proposes that a rat-specific hormonal mechanism (increased luteinizing hormone) underlies the LCT formation. The applicant also proposes that a rat-pecific mechanism (i.e., carbohydrate malabsorption) explains the imbalance in observed RTT and pheochromocytoma in rats treated with canagliflozin. Further details of nonclinical carcinogenicity studies can be found in Dr. Fred Alavi's review in this briefing document. Based on this nonclinical finding, pheochromocytomas, RCC, and LCT were evaluated throughout Phase 3 program for canagliflozin.

In the clinical program for dapagliflozin, another SGLT2 inhibitor, an imbalance in breast and bladder cancers were noted in subjects receiving dapagliflozin. This was an unexpected finding given that there were no nonclinical or clinical findings to suggest that SGLT2 inhibition would lead to breast or bladder cancer. The occurrence of breast and bladder cancers were followed throughout Phase 3 program for canagliflozin.

Since cancer has long latency period and occurs at relatively low incidence during clinical development program, analyses for these five cancers were based on all data from clinical trials regardless of rescue therapy. All events were reported, regardless of time to last dose of study drug.

As of the most recent update, data cutoff date of November 15, 2012, there are no reported cases of pheochromocytoma or malignant adrenal tumors in the canagliflozin development program.

One case of testicular cancer (seminoma, a germ cell tumor of the testes) was reported in a MTPC-sponsored trial, TA-7284-06, in a 48-year old man two months after starting treatment with canagliflozin 100 mg. This patient had an enlarged scrotum for a year prior to trial initiation and had complained of scrotal pain during the month prior to trial entry. The prior noted scrotal abnormality and the short latency period is not consistent with a drug-related causality.

The incidences of renal, bladder, and breast cancers with the exposure adjusted incidence rate are presented in Table 21 by treatment group. The overall incidence of these cancers was low in the clinical program for canagliflozin, and did not show an increased incidence of these cancers in the canagliflozin treatment groups compared to the non-canagliflozin treatment group as of November 15, 2012.

Table 21: Renal, Bladder, and Breast Cancer in All Phase 3 Trials of Canagliflozin through November 15, 2012 - Regardless of Rescue

Treatment arm	Cana 100 mg	Cana 300 mg	All Non-Cana
N	3139	3509	3640
Renal Cancer			
Subjects with AE, n (%)	2 (0.06)	3 (0.09)	3 (0.08)
Incidence Rate per 1000 PY	0.44	0.63	0.63
Bladder Cancer			
Subjects with AE, n (%)	2 (0.06)	3 (0.09)	4 (0.11)
Incidence Rate per 1000 PY	0.44	0.63	0.84
Breast Cancer			
N	1313	1514	1501
Subjects with AE, n (%)	5 (0.38)	7 (0.46)	6 (0.4)
Incidence Rate per 1000 PY	2.61	3.39	3.05

Source: Applicant response to Information Request, submission dated November 28, 2012, Tables 1, 2, 3

3.4 Osmotic Diuresis

Because canagliflozin increases urinary glucose excretion, it acts as an osmotic diuretic with an increase in urine output. Phase 1 trials have shown that there is an increase in urine output as soon as Day 1. The applicant used the following MedDRA Preferred Terms (PT) to identify and evaluate the clinical importance of diuresis related events with canagliflozin: PTs related to increase in urine output such as increase in urine frequency [pollakiuria (i.e., abnormally frequent urination), micturition urgency, or micturition disorder], urine output (PTs of polyuria or urine output increased), and night time micturition (PT of nocturia), as well as those related to thirst (PTs of thirst, polydipsia, dry mouth, throat dry, or tongue dry).

The Placebo-Controlled Studies Dataset (DS1) was the primary dataset for adverse event analysis, but these preferred term were also assessed in the Moderate Renal Impairment Dataset (DS2) to evaluate the impact of these adverse event in this patient population who are more sensitive to diuretic effect. In addition, in order to evaluate the clinical impact of these events in a larger population over a longer duration, the Broad Dataset (DS3) was also analyzed. All the data presented below represents incidence regardless of rescue.

<u>Placebo-Controlled Studies Dataset (DS1)</u>

A significantly higher incidence of osmotic diuresis-related adverse events were reported in the canagliflozin treatment group (6.7% and 5.6% in 100 and 300 mg dosing group respectively) compared to placebo group (0.8%). The incidence was not dose-dependent. The most reported PTs were pollakiuria, thirst, and polyuria. None of the events were serious, and three subjects in the canagliflozin group (2 subjects in 300 mg and 1 subject in 100 mg group) discontinued due to osmotic diuresis-related pollakiuria.

Table 22: Osmotic Diuresis-Related Adverse Events in DS1 - Regardless of Rescue

	Placebo (N=646)	Cana 100 (N=833)	Cana 300 (N=834)	Cana Total (N=1667)
Any osmotic diuresis AE, n (%)	5 (0.8)	56 (6.7)	47 (5.6)	103 (6.2)
Serious AE, n (%)	0	0	0	0
Osmotic diuresis leading to discontinuation, n (%)	0	1 (0.1)	2 (0.2)	3 (0.2)
Incidence rate per 100 subject-years exposure	2	14	12	13
Polyuria/Pollakiuria Reported Terms, n (%):	5 (0.8)	44 (5.3)	38 (4.6)	82 (4.9)
Micturition Urgency	0	2 (0.2)	3 (0.4)	5 (0.3)
Nocturia	1 (0.2)	3 (0.4)	1 (0.1)	4 (0.2)
Pollakiuria	4 (0.6)	35 (4.2)	26 (3.1)	61 (3.7)
Polyuria	0	6 (0.7)	12 (1.4)	18 (1.1)
Urine Output Increased	0	1 (0.1)	1 (0.1)	2 (0.1)
Thirst Reported Terms, n (%):	1 (0.2)	23 (2.8)	19 (2.3)	42 (2.5)
Dry Mouth	0	6 (0.7)	2 (0.2)	8 (0.5)
Polydipsia	0	6 (0.7)	2 (0.2)	8 (0.5)
Thirst	1 (0.2)	11 (1.3)	16 (1.9)	27 (1.6)

Source: ISS, Table 113

Moderate Renal Impairment Dataset (DS2)

The incidence of osmotic diuresis-related adverse event was slightly higher in the canagliflozin 100 mg treatment group (4.1%) compared to canagliflozin 300 mg (3.8%) or placebo (3.7%), as shown in Table 23. The incidence of osmotic diuresis-related events did not increase in DS2 compared to DS1; however, the number of subjects in DS2 are smaller. None of the events were serious or led to discontinuation. Similar to DS1, pollakiuria and thirst were most commonly reported adverse event terms.

Table 23: Osmotic Diuresis-Related Adverse Events in DS2 - Regardless of Rescue

	Placebo (N=382)	Cana 100 (N=338)	Cana 300 (N=365)	Cana Total (N=703)
Any osmotic diuresis AE, n (%)	14 (3.7)	14 (4.1)	14 (3.8)	28 (4.0)
Serious AE, n (%)	0	0	0	0
Osmotic diuresis leading to discontinuation, n (%)	0	0	0	0
Incidence rate per 100 subject-years exposure	5	6	5	6
Polyuria/Pollakiuria Reported Terms, n (%):	12 (3.1)	12 (3.6)	11 (3.0)	23 (3.3)
Micturition Urgency	0	3 (0.9)	3 (0.8)	6 (0.9)
Nocturia	2 (0.5)	1 (0.3)	0	1 (0.1)
Pollakiuria	7 (1.8)	7 (2.1)	9 (2.5)	16 (2.3)
Polyuria	2 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Urine Output Increased	1 (0.3)	3 (0.9)	2 (0.5)	5 (0.7)
Thirst Reported Terms, n (%):	2 (0.5)	4 (1.2)	4 (1.1)	8 (1.1)
Dry Mouth	2 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Thirst	0	3 (0.9)	4 (1.1)	7 (1.0)

Source: ISS, Table 114, 115

Broad Dataset (DS3)

The incidence of osmotic diuresis-related adverse events was higher in the canagliflozin treatment groups (6.8% and 7.1% with 100 mg and 300 mg respectively) compared to placebo

(1.9%) without dose-dependency, as shown in Table 24. None of the events were serious, and 16 subjects (0.3%) in the combined canagliflozin group and 1 subject (<0.1%) in the non-canagliflozin group discontinued due osmotic diuresis-related adverse event. Similar to DS1, the most commonly reported terms were pollakiuria, thirst, and polyuria.

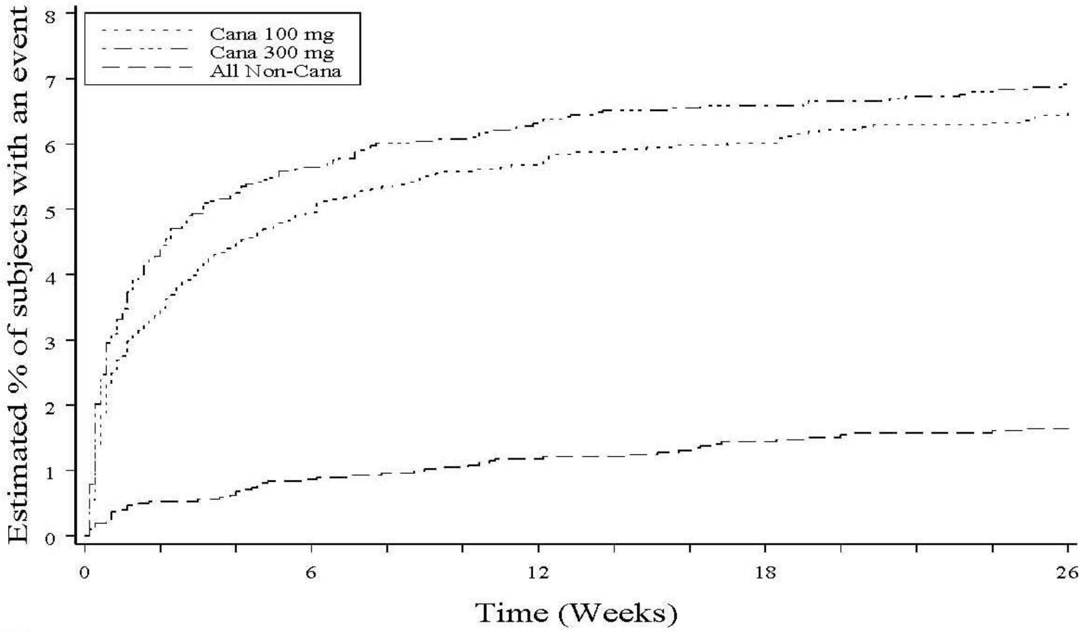
Table 24: Osmotic Diuresis-Related Adverse Events in DS3 - Regardless of Rescue

	Non-Cana (N=3262)	Cana 100 (N=3092)	Cana 300 (N=3085)	Cana Total (N=6177)
Any osmotic diuresis AE, n (%)	62 (1.9)	210 (6.8)	219 (7.1)	429 (6.9)
Serious AE, n (%)	0	0	0	0
Osmotic diuresis leading to discontinuation, n (%)	1 (<0.1)	7 (0.2)	9 (0.3)	16 (0.3)
Incidence rate per 100 subject-years exposure	3	9	10	10
Polyuria/Pollakiuria Reported Terms, n (%):	48 (1.5)	174 (5.6)	177 (5.7)	351 (5.7)
Micturition Disorder	1 (<0.1)	1 (<0.1)	0	1 (<0.1)
Micturition Urgency	5 (0.2)	16 (0.5)	15 (0.5)	31 (0.5)
Nocturia	10 (0.3)	14 (0.5)	13 (0.4)	27 (0.4)
Pollakiuria	26 (0.8)	105 (3.4)	125 (4.1)	230 (3.7)
Polyuria	8 (0.2)	30 (1.0)	32 (1.0)	62 (1.0)
Urine Output Increased	1 (<0.1)	19 (0.6)	14 (0.5)	33 (0.5)
Thirst Reported Terms, n (%):	16 (0.5)	80 (2.6)	78 (2.5)	158 (2.6)
Dry Mouth	11 (0.3)	30 (1.0)	14 (0.5)	44 (0.7)
Dry Throat	2 (0.1)	1 (<0.1)	0	1 (<0.1)
Polydipsia	1 (<0.1)	11 (0.4)	5 (0.2)	16 (0.3)
Thirst	2 (0.1)	42 (1.4)	64 (2.1)	106 (1.7)

Source: ISS, Table 116, 117

In both canagliflozin groups, the majority of osmotic diuresis related adverse events occurred during the first 6 weeks of study and appear to plateau, as shown in the Kaplan-Meier curve in Figure 1 for DS3. The median duration of these adverse events was similar in the non-canagliflozin group (69 days) and canagliflozin group (73 and 62 days in 100 mg and 300 mg group respectively).

Figure 1: Kaplan-Meier Plot of Time to First Osmotic Diuresis Related Event in DS3



No. Subjects at Risk					
Cana 100 mg	3092	2915	2811	2722	2386
Cana 300 mg	3085	2882	2750	2666	2314
All Non-Cana	3262	3208	3081	2960	2519

Source: ISS, Figure 12

Thus, osmotic diuresis related adverse events was increased in the canagliflozin treatment group compared to the comparator group, without dose-dependency, and the incidence did not appear to increase in subjects with moderate renal function (DS2) or with longer duration of follow up (DS3).

3.5 Volume Depletion Events Related to Reduced Intravascular Volume

As an osmotic diuretic, canagliflozin could also lead to adverse events related to reduced intravascular volume. The following Preferred Terms that could potentially indicate reduced intravascular volume were pre-specified for analysis: blood pressure decreased, dehydration, diastolic hypotension, dizziness postural, hypotension, hypovolemia, hypovolemic shock, orthostatic blood pressure decreased, orthostatic hypotension, orthostatic intolerance, postural orthostatic tachycardia syndrome, presyncope, shock, syncope, and urine output decreased.

DS1 was the primary dataset for adverse event analysis, and results from DS2, DIA3008, and DS3 are also evaluated in order to provide information regarding volume depletion-related adverse events in older subjects, subjects with diminished renal function, and diabetic complications and co-morbidities,

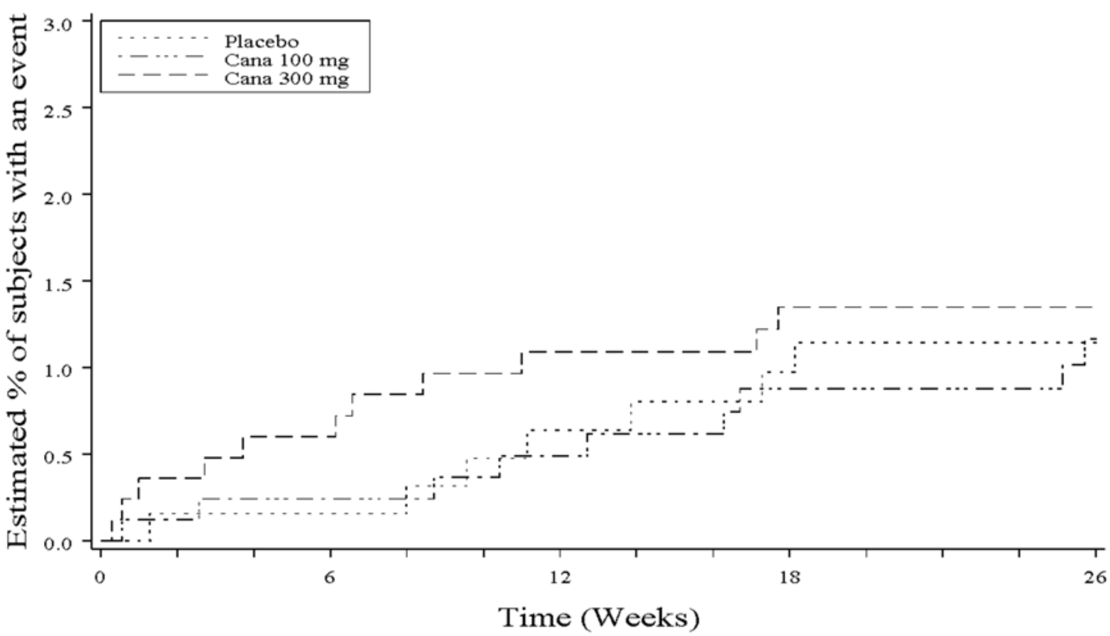
<u>Placebo-Controlled Studies Dataset (DS1)</u>

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. The incidence rate per 100 subject-years of exposure was 2.6, 2.8, and 2.4 for canagliflozin 100 mg, 300 mg, and placebo groups respectively. No subjects in the canagliflozin treatment group had volume depletion adverse events that were serious or led to discontinuation. The most commonly reported PT were hypotension (8 [0.5%] subjects in the combined canagliflozin group and 4 [0.6%] in the placebo group), dizziness postural (7 [0.4%] subjects in the combined canagliflozin group and 2 [0.3%] subjects in the placebo group), and orthostatic hypotension (4 [0.5%] in the canagliflozin 300 mg group and 1 [0.2%] subject in the placebo group). One subject in canagliflozin 100 mg group reported syncope.

The median time to onset of volume depletion adverse event was shorter in canagliflozin 300 mg group (43 days) compared to canagliflozin 100 mg group (102 days) or placebo group (78 days). In addition, 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 Kaplan-Meier curve of volume depletion adverse event (Figure 2) showed that the higher incidence in the canagliflozin 300 mg group compared to canagliflozin 100 mg or placebo groups occur for about 18 weeks, after which difference between treatment groups narrowed.

Figure 2: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DS1



No. Subjects at Risk

Placebo	646	638	607	577	393
Cana 100 mg	833	823	785	754	546
Cana 300 mg	834	820	788	757	534

Source: ISS, Figure 13

<u>Moderate Renal Impairment Dataset (DS2)</u>

The overall incidence of volume depletion adverse events was higher in DS2 compared to DS1, and was higher in the canagliflozin groups compared to the placebo group as shown in Table 25, showing dose-relationship. Similar to DS1, the canagliflozin treatment group showed an increase in the specific adverse events of dizziness postural, hypotension, and orthostatic hypotension. More syncope was reported with canagliflozin 300 mg in DS2 (three events) compared to DS1 (none).

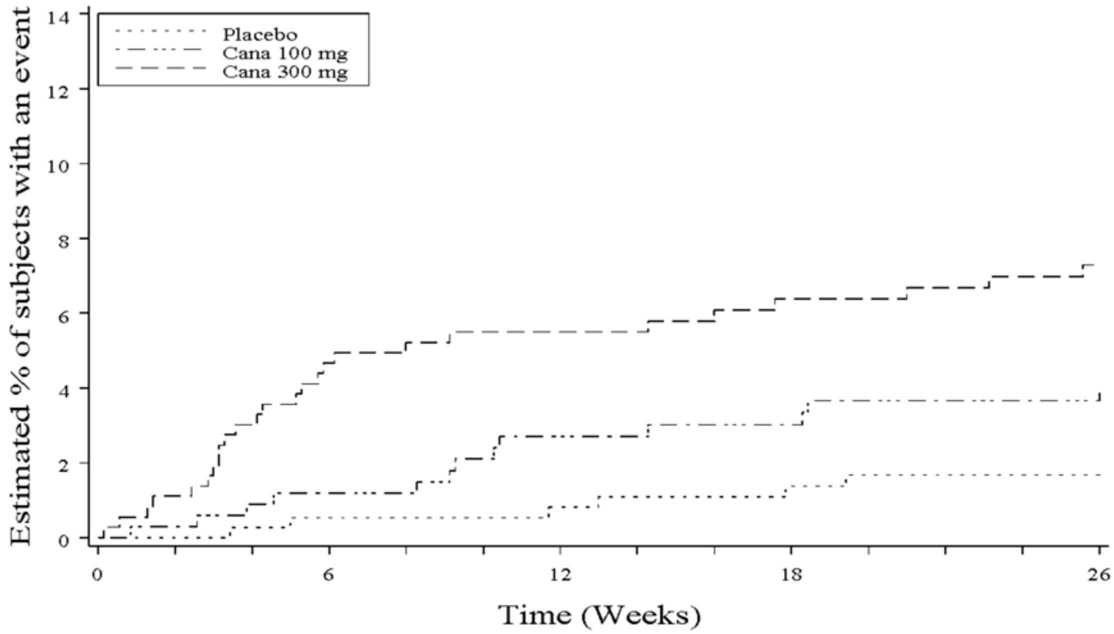
Table 25: Volume Depletion Adverse Events in DS2 - Regardless of Rescue

	Placebo (N=382)	Cana 100 (N=338)	Cana 300 (N=365)	Cana Total (N=703)
Any volume depletion AE, n (%)	10 (2.6)	17 (5.0)	31 (8.5)	48 (6.8)
Serious AE of volume depletion, n (%)	5 (1.3)	1 (0.3)	3 (0.8)	4 (0.6)
Volume depletion leading to discontinuation, n (%)	0	1 (0.3)	2 (0.5)	3 (0.4)
Incidence rate per 100 subject-years exposure	3.8	7.0	11.9	9.5
Reported Terms, n (%):				
Dehydration	2 (0.5)	1 (0.3)	4 (1.1)	5 (0.7)
Dizziness Postural	2 (0.5)	7 (2.1)	7 (1.9)	14 (2.0)
Hypotension	3 (0.8)	7 (2.1)	14 (3.8)	21 (3.0)
Orthostatic Hypotension	1 (0.3)	1 (0.3)	3 (0.8)	4 (0.6)
Presyncope	1 (0.3)	0	1 (0.3)	1 (0.1)
Syncope	2 (0.5)	1 (0.3)	3 (0.8)	4 (0.6)

Source: ISS, Table 121, 122

Similar to DS1, the median time to onset of volume depletion adverse event was shorter with canagliflozin 300 mg (40 days) compared to canagliflozin 100 mg (73 days) or placebo (131 days). Again, more subjects in the canagliflozin treatment groups, particularly with 300 mg dose, had volume depletion-related adverse events within the first 30 days of treatment (13 [3.6%] subjects in canagliflozin 300 mg, 3 [0.9%] subjects in canagliflozin 100 mg, and 1 [0.3%] subject in placebo group). This trend can be seen in the Kaplan-Meier curve for DS2 (Figure 3). However, unlike the Kaplan-Meier curve for DS1 (Figure 2), the difference between treatment group does not narrow over time.

Figure 3: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DS2



No. Subjects at Risk					
Placebo	382	376	356	343	295
Cana 100 mg	338	330	318	305	259
Cana 300 mg	365	348	329	317	266

Source: ISS, Figure 14

Broad Dataset (DS3)

As a reminder, the Broad Dataset (DS3) included a large pooled dataset from Phase 3 trials and the largest contribution of subjects is from DIA3008 trial. As a result, the overall population in DS3 compared to DS1 were older with longer duration of diabetes, with declining renal function and higher incidence of diabetes complications and co-morbidities.

In DS3, the incidence of volume depletion adverse events was higher in the canagliflozin groups, and showed dose-relationship similar to DS2, as displayed in Table 26. The volume depletion adverse events that were serious or led to discontinuation were not notably different between treatment groups. Similar to DS1 and DS2, the increase in the incidence of volume depletion-related adverse events were due to dizziness postural, hypotension, and orthostatic hypotension.

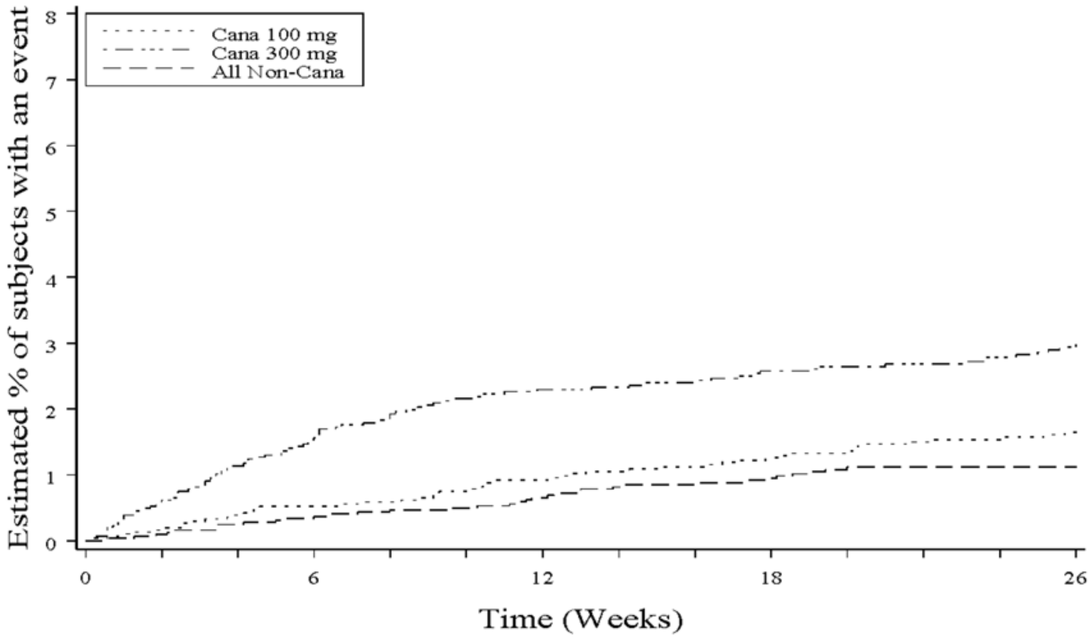
Table 26: Volume Depletion Adverse Events in DS3 - Regardless of Rescue

	Non-Cana (N=3262)	Cana 100 (N=3092)	Cana 300 (N=3085)	Cana Total (N=6177)
Any volume depletion AE, n (%)	49 (1.5)	71 (2.3)	105 (3.4)	176 (2.8)
Serious AE of volume depletion, n (%)	9 (0.3)	6 (0.2)	4 (0.1)	10 (0.2)
Volume depletion leading to discontinuation, n (%)	2 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Incidence rate per 100 subject-years exposure	2.2	3.1	4.8	3.9
Reported Terms, n (%):				
Blood Pressure Decreased	1 (<0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Dehydration	7 (0.2)	5 (0.2)	11 (0.4)	16 (0.3)
Dizziness Postural	13 (0.4)	18 (0.6)	24 (0.8)	42 (0.7)
Hypotension	13 (0.4)	34 (1.1)	47 (1.5)	81 (1.3)
Orthostatic Hypotension	4 (0.1)	7 (0.2)	19 (0.6)	26 (0.4)
Orthostatic Intolerance	0	1 (<0.1)	0	1 (<0.1)
Presyncope	5 (0.2)	3 (0.1)	2 (0.1)	5 (0.1)
Syncope	10 (0.3)	6 (0.2)	12 (0.4)	18 (0.3)

Source: ISS, Table 126, 127

Similar to DS1 and DS2, the median time to onset of volume depletion adverse event was shorter with canagliflozin 300 mg (46 days) compared to canagliflozin 100 mg (117 days) or non-canagliflozin (91 days). Again, more subjects in the canagliflozin treatment groups, particularly with 300 mg, had volume depletion-related adverse events within the first 30 days of treatment (38 [1.2%] in canagliflozin 300 mg, 14 [0.5%] in canagliflozin 100 mg, and 9 [0.3%] in non-canagliflozin group). The Kaplan-Meier curve of time to first volume depletion adverse event for DS3 is shown in Figure 4, and the higher incidence with canagliflozin 300 mg compared to canagliflozin 100 mg or placebo persisted over 26 weeks.

Figure 4: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DS3



No. Subjects at Risk					
Cana 100 mg	3092	3051	2955	2862	2513
Cana 300 mg	3085	3008	2864	2771	2407
All Non-Cana	3262	3224	3096	2973	2533

Source: ISS, Figure 16

The median duration of volume depletion adverse events was longer in the canagliflozin 300 mg group (6 days) compared to canagliflozin 100 mg group (2 days) and non-canagliflozin group (2 days).

When examining changes in concomitant anti-hypertensive medications including diuretics within 60 days of volume depletion-related adverse event, a higher proportion of subjects in the canagliflozin treatment groups (62 to 68% in 100 mg and 300 mg respectively) modified their blood-pressure lowering drugs compared to the non-canagliflozin group (43%). In comparison, in subjects who did not have volume depletion adverse events, fewer subjects (8%) modified their blood-pressure lowering drugs over a similar 60-day time period (using the median day of onset [Day 67] of the volume depletion adverse events in the combined canagliflozin group as the start date). The number of subjects who modified their diuretics within 60 days of volume depletion event were not notably different between treatment arms.

Table 27: Subjects with Change in Selected Concomitant Medications in DS3

	Subjects with volume depletion adverse events; change in selected concomitant medications within 60 days after onset of event			Subjects with no volume depletion adverse events; change in selected concomitant medications between Day 67 and 127		
Treatment Group	Non-Cana	Cana 100	Cana 300	Non-Cana	Cana 100	Cana 300
Total N	49	71	105	3213	3021	2980
Blood-pressure lowering drugs, n (%)	21 (43%)	44 (62%)	71 (68%)	353 (11%)	246 (8%)	235 (8%)
Loop diuretics, n (%)	7 (14%)	5 (7%)	14 (13%)	43 (1%)	20 (1%)	30 (1%)
Non-loop diuretics only, n (%)	7 (14%)	12 (17%)	23 (22%)	81 (3%)	62 (2%)	56 (2%)

Source: ISS, Table 129, 130

Since volume depletion adverse events are related to the diuretic action of canagliflozin, the overlap of osmotic diuresis-related events with volume depletion-related events was evaluated. As shown in Table 28, a higher proportion of subjects in the combined canagliflozin group experienced volume depletion-related adverse events in subjects with osmotic diuresis-related adverse event (6.8%), compared to subjects without osmotic diuresis-related adverse event (2.6%). The overlap of diuresis and volume-depletion events showed dose-relationship, as 3.8% and 9.6% of subjects with canagliflozin 100 mg and 300 mg respectively had both diuresis and volume depletion events.

Table 28: Volume Depletion Adverse Events in Subjects With Diuresis-Related Adverse Events in DS3 - Regardless of Rescue

	Non-Cana	Cana 100	Cana 300	Cana Total
Subjects with diuresis-related adverse events, n	62	210	219	429
Subjects with diuresis and volume depletion adverse event, n (%)	1 (1.6%)	8 (3.8%)	21 (9.6%)	29 (6.8%)
Subjects who did not have diuresis-related adverse event, n	3200	2882	2866	5748
Subjects with no diuresis and volume depletion adverse event, n (%)	48 (1.5%)	63 (2.2%)	84 (2.9%)	147 (2.6%)

Source: ISS, Table DAE45BC_03, DAE45BCC_03

In order to assess risk factors for volume depletion-related adverse events, subgroup analyses based on baseline characteristics are evaluated, as shown on Table 29. Subjects with low baseline eGFR (<60 mL/min/1.73m^2) had an increased, dose-related risk of volume depletion adverse events. Concomitant use of ACE inhibitors or ARB or diuretics also demonstrated dose-related increase in the incidence of volume depletion adverse events. Higher risk of volume depletion was also seen in elderly (≥65 years of age) compared to younger subjects, and this increase in the incidence of volume depletion events were more prominent in subjects ≥75 years of age compared to <75 years of age.

A higher, dose-related risk was also seen in male subjects, subjects with higher baseline HbA1c levels (>7.9%), lower systolic blood pressure (≤110 mmHg), and subjects with diabetic complications and longer duration of diabetes (≥10 years).

Table 29: Subjects with Volume Depletion Adverse Events by Baseline Characteristics in DS3 - Regardless of Rescue

	% (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)

[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.
[c] Includes both loop and non-loop diuretics.
Source: ISS, Table 131

Since use of loop diuretics and low eGFR may potentially overlap, the effect of combining these two factors on the incidence of volume depletion events was assessed. As shown in Table 30, an

increase in the incidence of volume depletion events in subjects with both factors (e.g., eGFR <60 and use of loop diuretics) compared to those with only one of these factors was only appreciably seen with canagliflozin 300 mg.

Table 30: Subjects with Volume Depletion Adverse Events by eGFR and Use of Loop Diuretics at Baseline in DS3 - Regardless of Rescue

		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)

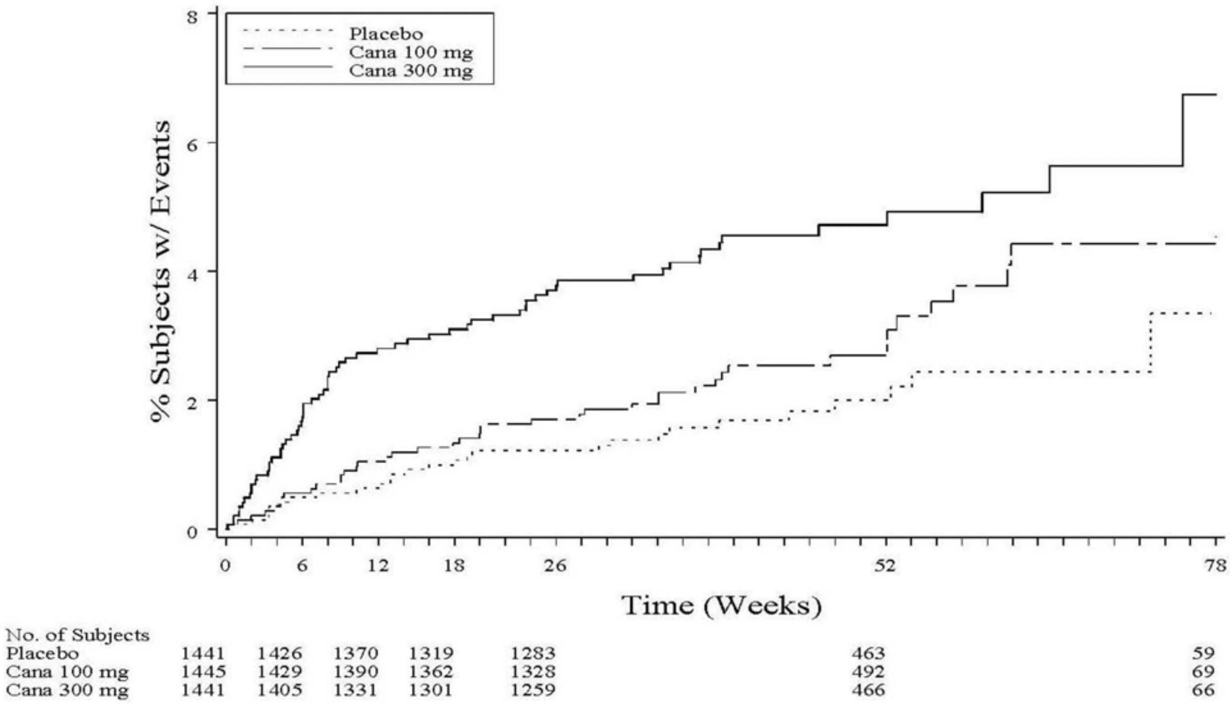
[a] Incidence of volume depletion adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP.
[b] Number of subjects in the Safety Analysis Set with the baseline characteristic.

Source: ISS, Table 132

Based on this subgroup analyses, the applicant propose labeling the starting canagliflozin dose of 100 mg for subjects on loop diuretics, moderate renal impairment, and ≥75 years of age, with titration to 300 mg dose if additional glycemic control is needed. It should be noted that although subgroup analyses showed that subjects with these factors are at higher risk for developing volume depletion-related event, there was no study to evaluate whether this titration of dose would reduce the risk of volume depletion-related adverse events in these subjects.

Subjects in DIA3008 contribute a large portion of DS3, and subjects enrolled in DIA3008 are likely to be affected by the volume depletion-related events given that the subjects in this trial are older with declining renal function. In DIA3008, the incidence of volume depletion adverse events was 2.8% (41/1445), 4.6% (66/1441), and 1.9% (27/1441) of subjects with canagliflozin 300 mg, 100 mg, and placebo. Based on the Kaplan-Meier analysis of time to first volume depletion event, the hazard ratio for volume depletion event was 1.5 (95% CI:0.91,2.40) with canagliflozin 100 mg and 2.5 (95% CI:1.58,3.86) with canagliflozin 300 mg. Figure 5 shows the Kaplan-Meier curve for DIA3008.

Figure 5: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DIA3008 Interim Analysis



Source: ISS, Figure 15

3.6 Renal Safety

As discussed, 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 order to evaluate renal changes induced by canagliflozin, subjects were regularly monitored for their renal function throughout Phase 3 trials. Pre-specified renal-related adverse events were prospectively defined, collected, and adjudicated by a blinded endpoint committee in the entire Phase 3 program. In addition, the applicant conducted a dedicated Phase 3 efficacy trial (DIA3004) in subjects with moderate renal impairment who had an estimated GFR ranging from 30 to less than 50 mL/min/1.73m^2 at study entry. At NDA submission, DIA3004 data up to Week 26 was provided. The controlled extension period of DIA3004 is still ongoing, and upon study completion will provide further information about safety of canagliflozin in this population.

Due to renal-related concern with canagliflozin, we consulted the Division of Cardiovascular and Renal Products (DCRP) for a review of renal safety findings associated with canagliflozin. Renal-related findings are briefly summarized here, and are discussed in more detail in Dr. Aliza Thompson's review.

In Phase 3 program with canagliflozin, there was an early and dose-dependent decreases in eGFR in Phase 3 trials with corresponding changes in serum creatinine and BUN. In the Placebo-controlled Studies Dataset (DS1), this early drop in eGFR did not appear to worsen over time. However, decline in eGFR persisted through to the end of follow-up in DIA3004 and DIA3008, and as previously discussed, DIA3004 and DIA3008 enrolled subjects with moderate renal function in comparison to DS1 which enrolled subjects with normal to mild renal function. There was also an imbalance in the predefined limits of change (PDLC) criteria for eGFR with canagliflozin. Similar to change in eGFR, the PDLC of eGFR, which indicate more marked changes in renal function, was greater in both 100 mg and 300 mg dose of canagliflozin compared to placebo in the Moderate Renal Impairment Dataset (DS2). Finally, the incidence of renal related adverse events was greater with canagliflozin, and higher incidence of renal-related events were observed with both 100 mg and 300 mg doses in DS2 when compared to placebo.

Please refer to Dr. Aliza Thompson's review for further details.

3.7 Hemoconcentration and Thromboembolic Events

<u>Hematology</u>

Small mean percent increases in hemoglobin concentration and hematocrit occurred at the initial assessment timepoint (Week 6) and persisted through Week 26 in DS1, as summarized in Table 31. The mean percent increases in hemoglobin were 3.5% and 3.8% in canagliflozin 100 mg and 300 mg group respectively, compared to a slight decrease in the placebo group (-1.1%). Similar increases in hematocrit were also observed. No significant changes in platelet count were observed.

Table 31: Selected Hematology Laboratory Values in DS1 - Regardless of Rescue

	Placebo	Cana 100 mg	Cana 300 mg
Blood Hematocrit (%)	507	703	711
Mean baseline	42.5	41.9	42.0
Mean change from baseline at Week 26	0.1	2.4	2.6
Mean % change	*0.2%*	*5.7%*	*6.2%*
Blood Hemoglobin (g/dL)	509	706	716
Mean baseline	14.2	14.1	14.1
Mean change from baseline at Week 26	-0.2	0.5	0.5
Mean % change	*-1.4*	*3.5%*	*3.5%*
Blood Platelet (x10E3/uL)	503	697	699
Mean baseline	265.3	265.2	269.4
Mean change from baseline at Week 26	-1.8	-3.6	-7.7
Mean % change	*-0.7%*	*-1.4%*	*-2.9%*

Source: ISS, DLAB01C_01

<u>Thromboembolic Events</u>

No venous thromboembolic (VTE) events such as deep vein thrombosis or pulmonary embolism occurred in Phase 1 or 2 trials.

Throughout Phase 3 trials, VTE events were independently adjudicated by an EAC. VTE events were identified using a Standard MedDRA Query (SMQ) of 'embolic and thrombotic events, venous'. A total of 21 potential VTE events were identified at the time of NDA submission throughout all Phase 3 trials, including three fatal events that were adjudicated as CV deaths. Of 21 VTE events, one was not treatment-emergent since it occurred more than 30 days off study drug. Two subjects were not confirmed to be VTE events (subjects 400873 and 804929). The remaining 18 events confirmed by EAC as VTE events are summarized in Table 32 and listed in Table 33. Of these 18 VTE events, 16 were serious, and one event led to study drug discontinuation.

Table 32: Summary of Venous Thromboembolic Events, Regardless of Rescue - DS4

	Cana 100	Cana 300	Non-Cana
VTE events, n (%)	5 (0.2)	8 (0.3)	5 (0.2)
Serious VTE events, n (%)	4 (0.1)	8 (0.3)	4 (0.1)
Incidence per 100 subject-years	0.15	0.24	0.15
Preferred Term:			
Cardiac death	0	1 (<0.1)	0
Deep vein thrombosis	3 (0.1)	3 (0.1)	3 (0.1)
Pulmonary embolism	2 (0.1)	5 (0.2)	3 (0.1)
Venous thrombosis	0	1 (<0.1)	1 (<0.1)
Venous thrombosis limb	0	1 (<0.1)	0

Source: ISS, Tables 187, 188

Table 33: Listing of Adjudicated VTE Events

Trial	Subject	Treatment Group	Event	Onset Day	Other potential precipitating factor
DIA3002	200184	Cana 300 mg	DVT	157	
DIA3002	200420	Placebo	DVT	225	
DIA3004	400104	Cana 300 mg	DVT, PE	143	
DIA3004	400138	Cana 100 mg	DVT	371	
DIA3004	400536	Placebo	DVT	226	prolonged immobilization due to injury
DIA3005	500161	Cana 300 mg	DVT	122	
DIA3005	500252	Cana 100 mg	PE, thrombosis	134	
DIA3008	(b) (4)	Cana 300 mg	PE	578	
DIA3008		Cana 100 mg	DVT	492	immobilization due to fracture before the event
DIA3008		Cana 100 mg	DVT	393	was hospitalized for hemorrhagic stroke
DIA3008		Placebo	PE	156	was hospitalized for contusion
DIA3008		Cana 100 mg	DVT, PE	85	
DIA3008		Cana 300 mg	DVT, PE	361	
DIA3008		Cana 300 mg	PE	5	
DIA3008		Cana 300 mg	PE, venous thrombosis	184	underwent hysterectomy 15 days before the event
DIA3008		Placebo	DVT, PE	345	
DIA3008		Cana 300 mg	PE	16	
DIA3008		Glimepiride	PE	284	underwent vertebral surgery 34 days before the event

Source: ISS, Narratives

The time to onset of VTE events appear to be shorter in the canagliflozin 300 mg group compared to 100 mg or placebo; the mean time to onset was 196 days in canagliflozin 300 mg (n=8), 295 days in 100 mg (n=5), and 247 days in non-canagliflozin (n=5). Two of 18 subjects had early VTE events within 30 days (Day 6 and 16), and both received canagliflozin 300 mg.

VTE events may be potentially precipitated by volume depletion events. However, among these subjects, only one subject (200184) also had volume-related event (hypotension) about 3 months before VTE event.

At 4MSU, two additional subjects reported VTE event, one subject each in canagliflozin 100 mg and non-canagliflozin group.

3.8 Bone Safety

In nonclinical studies of rats, an increase in trabecular bone volume (hyperostosis) was observed. Please refer to Dr. Alavi's review for details regarding nonclinical bone safety findings. Also, because of its mechanism of action, canagliflozin may potentially affect calcium and phosphorus homeostasis. Fractures as well as markers of bone metabolism were monitored and collected

throughout clinical development program of canagliflozin. Fractures were adjudicated by an independent blinded Fracture Adjudication Committee.

The Metabolic Bone Disease Team in the Division of Reproductive and Urology Products (DRUP) reviewed bone-related findings submitted with the NDA, which included assessment on calcium, phosphate and hormones regulating calcium metabolism, bone turnover markers, bone density measurement for the first 26-weeks of DIA3010, as well as incidences of fractures.

The clinical findings are briefly summarized here, and are discussed with more details in Dr. Stephen Voss's review.

There was no consistent clinically meaningful changes in serum or urine levels of calcium or phosphate in Phase 1 or Phase 2 trials. In a pooled dataset of all placebo-controlled Phase 3 trials (DS1), no meaningful change in serum calcium levels were observed. A small to moderate percent increase in serum phosphate was observed with canagliflozin treatment compared to placebo after 26 weeks, and this increase appeared to be dose related (3.6%, 5.1% and 1.5% with canagliflozin 100 mg, 300 mg, and placebo respectively). Changes in serum phosphate levels were seen in DIA3004 (trial in subjects with moderate renal impairment; mean percent increases of 5.0% and 9.3% with canagliflozin 100 mg and 300 mg respectively compared to 1.2% with placebo) and DIA3010 (trial in older subjects). Also in DIA3004, a moderate reduction in PTH (median % change from baseline of -3.6% and -8.2% with canagliflozin 100 mg and 300 mg respectively compared to 2.4% with placebo) and moderate mean increase in 25-hydroxyvitamin D was seen with canagliflozin treatment compared to placebo (mean % change from baseline of 18.6% and 22% with canagliflozin 100 mg and 300 mg respectively compared to 10.8% with placebo).

In DIA3010, the bone density by DXA from baseline at Week 26 showed no consistent trend in the lumbar spine (increase with canagliflozin 100 mg and decrease with 300 mg), slight decrease in the distal forearm, small increase in the femoral neck, and small decrease in total hip in the canagliflozin groups when compared to placebo.

In DIA3010, an increase in bone resorption marker (beta-CTx, LS mean % increase from baseline of 28.8% and 36.6% with canagliflozin 100 mg and 300 mg respectively compared to 11.8% with placebo) and a small decrease in the bone formation marker (P1NP; LS mean % increase from baseline of 2.7% and 1.5% with canagliflozin 100 mg and 300 mg respectively compared to 8.4% with placebo) were observed with canagliflozin treatment compared to placebo from baseline to Week 26. The controlled extension period of DIA3010 is still ongoing, and will provide bone density measurements at Week 52 and Week 104 upon study completion.

Throughout canagliflozin Phase 3 trials, all clinical fractures were adjudicated. The following briefly describe the observed imbalances in the pooled long-term dataset of all Phase 3 trials (DS4):

- A higher incidence of low trauma fractures in the canagliflozin groups compared to non-canagliflozin group:
    - A higher incidence of low trauma upper limb fractures in the canagliflozin groups compared to non-canagliflozin group.

- A time to event analysis of low trauma fractures showed more events in canagliflozin group compared to non-canagliflozin group within the first 12 weeks after randomization.
- A higher incidence of upper limb fractures in females in the canagliflozin groups compared to non-canagliflozin group.
- A higher incidence of fractures in DS4 dataset with moderate renal impairment (eGFR 30 to <60), with imbalance related to the upper limb fractures.

Please refer to Dr. Stephen Voss's review for further details.

3.9 Hepatic Safety

Liver function tests (LFTs) were conducted on all subjects at baseline and periodically thereafter throughout canagliflozin program. In Phase 3 trials, subjects were excluded from randomization if screening showed an alanine aminotransferase (ALT) level of >2x upper limit of normal (ULN). For subjects with an ALT ≥3x ULN during the trial, LFTs were to be repeated within 3 days, and subjects with confirmed ALT ≥3-5x ULN underwent biweekly LFT monitoring while remaining on treatment, whereas subjects with an ALT ≥5x ULN and subjects with an ALT ≥3x ULN and total bilirubin ≥2x ULN were discontinued from treatment.

Throughout clinical development of canagliflozin (Phases 1, 2, and 3), all cases meeting one of the following criteria were reviewed and adjudicated by an independent Hepatic Events Assessment Committee (HEAC) for an assessment of causality to study drug, type (hepatocellular, cholestatic, mixed or other) and severity (mild, moderate, severe, fatal) of the hepatic event, and to assess possible alternative etiologies:

1) ALT or aspartate aminotransferase (AST) ≥5x ULN
2) ALT or AST ≥3x ULN with concomitant rise in total bilirubin (TB) ≥2x ULN within 30 days after the initial qualifying ALT or AST increase
3) Any adverse events related to pre-specified liver-related Preferred Terms; this was developed from the serious liver injury SMQ

HEAC members, which included three external hepatology experts, remained blinded to treatment group assignment throughout the assessment process. The HEAC members classified causality to study drug using definitions provided in Table 34. Agreement between all three external experts for a single causality category was required; lack of consensus for causality required teleconference for HEAC members to determine final causality.

Table 34: Hepatic Event Causality Definitions

Definite	The drug is considered as the cause: clear time course, exclusion of other causes; typical pattern of drug-induced liver injury, positive rechallenge if available.
Probable	Chronological criteria are suggestive; the etiological work-up reasonably excludes other classical challenging causes; the study drug appears to be the most likely cause even if there is not specific clinical data suggesting specifically the role of a drug.
Possible	Some criteria are missing or there is a challenging diagnosis; e.g., another drug given within a compatible period; absence of ultrasound examination in a cholestatic/mixed pattern liver injury; absence of adapted viral screening in a cytolytic liver injury (HAV, HBV, HCV etc).
Unlikely	Another cause appears more likely or chronology for relationship to study drug is very atypical.
Excluded	Another cause is definitely responsible or time-course not compatible: e.g., ALT has already significantly increased before the initiation of treatment; or onset more than 8 weeks after discontinuation of the treatment.
Not assessable	Available data are too scant to allow a reasonable assessment: not clear chronology; not clear results for liver abnormalities; no data for the etiological assessment

Source: ISS-Appendix 7

Mean Percent Change from Baseline

In the Placebo-Controlled Studies Dataset (DS1), ALT and (AST) levels decreased from baseline over time with canagliflozin compared to placebo; the mean reductions in ALT from baseline at Week 26 were -7.5% and -11.1% with canagliflozin 100 mg and 300 mg respectively, compared to 2.7% with placebo. Similarly, AST and alkaline phosphatase levels decreased over time with canagliflozin treatment. However, there was a slight modest increase in serum bilirubin in Phase 3 trials with canagliflozin compared to placebo. In DS1, the mean percent change from baseline in serum bilirubin at Week 26 were 8% and 9.5% with canagliflozin 100 mg and 300 mg respectively, compared to 2.2% with placebo.

Predefined Limits of Change for Liver Function Tests

The predefined limits of change (PDLC) for ALT or AST elevations were based on any post-baseline double-blind treatment period and last on-treatment value (defined as a value up to two days after the last dose of study drug) meeting the PDLC criterion. The proportion of subjects that had PDLC criteria for ALT or AST elevations at any or last values were low with no significant difference between treatment groups in the Placebo-controlled Studies Dataset (DS1) or Moderate Renal Impairment Dataset (DS2). Therefore, results from the Broad Dataset (DS3) are discussed to assess significant elevations in liver enzymes in the overall Phase 3 program.

The proportion of subjects and incidence rates in person-years for elevations in ALT, AST, and ALT or AST for DS3 are shown in Table 35, Table 36, and Table 37 respectively. Data in DS3 showed that the proportion of subjects meeting the PDLC criteria for ALT and/or AST >3x and >5x ULN in any post-baseline value was higher with canagliflozin 100 mg compared to canagliflozin 300 mg and non-canagliflozin. Similarly, the exposure adjusted incidence rate, calculated per 1000 person-years exposure, also demonstrated a higher incidence of ALT and/or

AST elevations with canagliflozin 100 mg compared to canagliflozin 300 mg or non-canagliflozin. It is unclear why we observe a higher incidence of ALT and/or AST elevations with the lower dose of canagliflozin (100 mg) without similar or greater increased incidence with the higher dose of canagliflozin (300 mg).

Table 35: Number of Subjects with Serum ALT Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

Parameter Time Interval Pre-Defined Limits Of Change	Cana 100 mg n (%)	Cana 300 mg n (%)	All Cana n (%)	All Non-Cana n (%)
Serum Alanine Aminotransferase (U/L)				
ANY POST-BASELINE VALUE	3016	2969	5985	3160
ALT >3xULN	22 (0.7)	13 (0.4)	35 (0.6)	13 (0.4)
ALT >5xULN	11 (0.4)	3 (0.1)	14 (0.2)	3 (0.1)
ALT >8xULN	7 (0.2)	1 (<0.1)	8 (0.1)	1 (<0.1)
ALT >10xULN	4 (0.1)	1 (<0.1)	5 (0.1)	1 (<0.1)
ALT >20xULN	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
ALT >3xULN and Bilirubin >2xULN	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Incidence rate per 1,000 person-years exposure				
ALT >3xULN	9.77	5.92	7.87	5.74
ALT >5xULN	4.88	1.37	3.15	1.33
ALT >8xULN	3.11	0.46	1.80	0.44
ALT >10xULN	1.78	0.46	1.12	0.44
ALT >20xULN	0.44	0.46	0.45	0.00
ALT >3xULN and Bilirubin >2xULN	0.44	0.46	0.45	0.00
LAST POST-BASELINE VALUE	3016	2969	5985	3160
ALT >3 x ULN	10 (0.3)	3 (0.1)	13 (0.2)	6 (0.2)
ALT >5 x ULN	7 (0.2)	1 (<0.1)	8 (0.1)	1 (<0.1)
ALT >8 x ULN	4 (0.1)	1 (<0.1)	5 (0.1)	0

Note: ALT >3X ULN and Serum Bilirubin >2X ULN is composite criterion with the Serum Bilirubin elevation >2 X ULN within 30 days following the ALT elevation >3x ULN.

Note: Exposure adjusted incidence rates are per 1,000 person-years and calculated as 1,000*(the total number of subjects with an elevation divided by the total person-year exposure for all treated subjects who have a postbaseline lab value)

Source: ISS Table 177

Table 36: Number of Subjects with AST Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

Parameter Time Interval Pre-Defined Limits Of Change	Cana 100 mg n (%)	Cana 300 mg n (%)	All Cana n (%)	All Non-Cana n (%)
Serum Aspartate Aminotransferase (U/L)				
ANY POST-BASELINE VALUE	3010	2967	5977	3159
AST >3xULN	16 (0.5)	8 (0.3)	24 (0.4)	10 (0.3)
AST >5xULN	8 (0.3)	2 (0.1)	10 (0.2)	2 (0.1)
AST >8xULN	3 (0.1)	2 (0.1)	5 (0.1)	1 (<0.1)
AST >10xULN	2 (0.1)	2 (0.1)	4 (0.1)	0
AST >20xULN	1 (<0.1)	0	1 (<0.1)	0
AST >3xULN and Bilirubin >2xULN	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Incidence rate per 1,000 person-years exposure				
AST >3xULN	7.11	3.64	5.40	4.42
AST >5xULN	3.56	0.91	2.25	0.88
AST >8xULN	1.33	0.91	1.12	0.44
AST >10xULN	0.89	0.91	0.90	0.00
AST >20xULN	0.44	0.00	0.22	0.00
AST >3xULN and Bilirubin >2xULN	0.44	0.46	0.45	0.00
LAST POST-BASELINE VALUE	3010	2967	5977	3159
AST >3 x ULN	7 (0.2)	3 (0.1)	10 (0.2)	4 (0.1)
AST >5 x ULN	4 (0.1)	2 (0.1)	6 (0.1)	1 (<0.1)
AST >8 x ULN	2 (0.1)	2 (0.1)	4 (0.1)	0

Note: AST >3X ULN and Serum Bilirubin >2X ULN is composite criterion with the Serum Bilirubin elevation >2 X ULN within 30 days following the AST elevation >3x ULN.

Note: Exposure adjusted incidence rates are per 1,000 person-years and calculated as 1,000*(the total number of subjects with an elevation divided by the total person-year exposure for all treated subjects who have a postbaseline lab value)

Source: ISS Table 178

Table 37: Number of Subjects with Serum ALT or Serum AST Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

Parameter Time Interval Pre-Defined Limits Of Change	Cana 100 mg n (%)	Cana 300 mg n (%)	All Cana n (%)	All Non-Cana n (%)
Serum Alanine Aminotransferase (U/L)& Serum Aspartate Aminotransferase (U/L)				
ANY POST-BASELINE VALUE	3016	2969	5985	3160
ALT >3xULN or AST >3xULN	25 (0.8)	18 (0.6)	43 (0.7)	18 (0.6)
ALT >5xULN or AST >5xULN	12 (0.4)	4 (0.1)	16 (0.3)	4 (0.1)
ALT >8xULN or AST >8xULN	7 (0.2)	2 (0.1)	9 (0.2)	1 (<0.1)
ALT >10xULN or AST >10xULN	5 (0.2)	2 (0.1)	7 (0.1)	1 (<0.1)
ALT >20xULN or AST >20xULN	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
(ALT >3xULN and Bilirubin >2xULN) or (AST >3xULN and Bilirubin >2xULN)	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Incidence rate per 1000 person-years exposure				
ALT >3xULN or AST >3xULN	11.10	8.20	9.67	7.95
ALT >5xULN or AST >5xULN	5.33	1.82	3.60	1.77
ALT >8xULN or AST >8xULN	3.11	0.91	2.02	0.44
ALT >10xULN or AST >10xULN	2.22	0.91	1.57	0.44
ALT >20xULN or AST >20xULN	0.44	0.46	0.45	0.00
(ALT >3xULN and Bilirubin >2xULN) or (AST >3xULN and Bilirubin >2xULN)	0.44	0.46	0.45	0.00

Note: (ALT >3X ULN and Serum Bilirubin >2X ULN) or (AST >3X ULN and Serum Bilirubin >2X ULN) is composite criterion with the Serum Bilirubin elevation >2 X ULN within 30 days following the ALT or AST elevation >3x ULN.
Note: Exposure adjusted incidence rates are per 1000 person-years and calculated as 1000*(the total number of subjects with an elevation divided by the total person-year exposure for all treated subjects who have a postbaseline lab value)
Source: ISS Table 179

The proportion of subjects meeting the PDLC criteria for bilirubin was low and similar between treatment groups in DS1 and DS2. In DS3, 0.2% in the combined canagliflozin and 0.1% in non-canagliflozin group experienced any post-baseline value meeting PDLC criteria for bilirubin (>2x ULN), as shown in Table 38. Five subjects in combined canagliflozin group and no subjects in non-canagliflozin group had serum bilirubin value >2x ULN.

Table 38: Number of Subjects with Serum Bilirubin Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

	Cana 100 mg n (%)	Cana 300 mg n (%)	All Cana n (%)	All Non-Cana n (%)
Serum bilirubin (umol/l)				
Any post-baseline value	3016	2969	5985	3160
Bilirubin >2x ULN	2 (0.1)	7 (0.2)	9 (0.2)	4 (0.1)
Bilirubin > ULN and >25% increase from baseline	56 (1.9)	55 (1.9)	111 (1.9)	56 (1.8)
Last post-baseline value	3016	2969	5985	3160
Bilirubin >2x ULN	1 (<0.1)	4 (0.1)	5 (0.1)	0
Bilirubin > ULN and >25% increase from baseline	26 (0.9)	24 (0.8)	50 (0.8)	22 (0.7)

Note: Percentages calculated with the number of subjects per time interval as denominator
Source: ISS, Table 180

Events Adjudicated by HEAC

As of January 31, 2012, 56 subjects had hepatic events meeting adjudication criteria. Table 39 shows the distribution of events by adjudication criteria (excluding two subjects as noted). Forty-eight subjects met hepatic laboratory adjudication criteria and six subjects were reviewed based on hepatic adverse event terms. As noted, two subjects met the laboratory criteria but were not included in Table 39 since DIA3005 High Glycemic Cohort and Phase 1 trials were not included in the Safety Analysis Set. More hepatic events from canagliflozin 100 mg were submitted for adjudication compared to canagliflozin 300 mg or placebo groups.

Table 39: Summary of Cases Sent for HEAC Adjudication: Safety Analysis Set

HEAC criteria	Control n/N (%)	Cana 100 mg n/N (%)	Cana 300 mg n/N (%)
LFT criteria met*:	**11/3859 (0.29)**	**22/3249 (0.68)**	**15/3622 (0.41)**
ALT ≥5xULN	10/3859 (0.26)	20/3249 (0.62)	12/3622 (0.33)
AST ≥5xULN	5/3859 (0.13)	11/3249 (0.34)	10/3622 (0.28)
ALT or AST ≥3xULN followed by TB ≥2xULN	0	5/3249 (0.15)	3/3622 (0.08)
Pre-specified liver-related Preferred Terms	**1/3859 (0.03)**	**3/3249 (0.09)**	**2/3622 (0.06)**

*Subjects may have met more than 1 criteria.
NOTE: N is the total number of subjects from DS4 plus DIA3015 population for this hepatic adjudication (DS4 does not include subjects from DIA3015).
NOTE: Two subjects were excluded from this table: Subject 500611 (from DIA3005 High Glycemic Cohort; received canagliflozin 300 mg and had ALT and AST ≥5xULN) and 480007 (from Phase 1 trial DIA1006; received canagliflozin 200 mg and had ALT and AST ≥5xULN)
Source: ISS, Table 182

HEAC categorized hepatic events in 56 events as shown in Table 40. One subject in the non-canagliflozin group was assessed as probably-related; this subject had elevations in both ALT and AST >5x ULN. Across all treatment groups, eight cases were assessed as possibly-related.

Table 40: Summary of Causality Determined by HEAC

Treatment Group	Non-cana	Cana 100 mg	Cana 300 mg	Overall
Assessed Cases (N)	13	25	18	56
Categories				
Definite	0	0	0	0
Probable	1	0	0	1
Possible	3	3	2	8
Unlikely	4	11	6	21
Excluded	5	11	10	26

Source: SCS, Table 137 [including subject 500260]

In order to assess the potential for canagliflozin to cause severe liver injury (e.g., irreversible liver injury), we identified cases of Biochemical Hy's law where aminotransferase elevation was accompanied by increased serum total bilirubin (TB). There were eight cases meeting the laboratory criteria for Hy's Law (ALT or AST ≥3x ULN with TB ≥2x ULN), all with canagliflozin at NDA submission. For all eight cases, the blinded HEAC determined the causality as either unlikely or excluded. In our review of these eight cases, we agreed with the HEAC's causality assessment in six cases where the event was determined to be unlikely-related

to canagliflozin treatment since an alternative etiology for observed liver function changes were present in each of these cases (i.e., cholecystitis, adenocarcinoma, cholangiocarcinoma; Table 41).

Table 41: Eight Cases Meeting Adjudication Criteria of AST or ALT ≥3x ULN and Total Bililrubin ≥2x ULN

User Subject ID	Likely Alternative Etiology
400373	Bile duct stone
(b) (4)	Hepatitis E
120205	Cholecystitis, choledocholithiasis
(b) (4)	Adenocarcinoma
(b) (4)	Cholangiocarcinoma
150565	Cholelithiasis
(b) (4)	Unclear; see Dr. Seeff's narrative
(b) (4)	Unclear; see Dr. Seeff's narrative

We consulted Dr. Seeff from the Office of Surveillance and Epidemiology (OSE) to provide assessment for two unusual cases (subject (b) (4) and (b) (4)). Dr. Seeff agreed with the applicant's assessment of these two cases and concluded that liver events in these two cases were not instances of drug-induced liver injury (DILI) related to canagliflozin.

In addition, we asked Dr. Seeff to provide an assessment on additional 18 cases who did not meet Biochemical Hy's law but had significant elevation in aminotransferase at some point during the trials and where narratives lacked the necessary clinical information (i.e., serology) to completely exclude a role of canagliflozin in the reported hepatic events. Dr. Seeff concluded that two of 18 cases represented 'possible' DILI (602764 and 602830) based on the lack of complete clinical data.

In addition, two subjects from the Mitsubishi Tanabe Pharmaceutical Corporation Phase 3 trial (TA-7284-06) met HEAC adjudication criteria (both subjects met both criteria of ALT or AST ≥5x ULN and combined ALT ≥3x ULN and total bilirubin ≥2x ULN). Subjects from MTPC program do not undergo HEAC adjudication as the MTPC studies are being developed by the applicant's Japanese partner with a separate database to which the applicant does not have direct access. These two hepatic events are briefly summarized here:

- Subject T062301 is a 64-year old male with T2DM on mitiglinide and received canagliflozin 100 mg daily. At Week 28 visit, subject reported brown urine, itching, and lack of energy. Laboratory values showed elevated liver enzymes, with ALT 545 U/L, AST 132 U/L, total bilirubin 18.7 mg/dL and alkaline phosphatase 1084 U/L. The subject was diagnosed with portal hepatitis bile duct cancer by CT scan and was hospitalized.
- Subject T060404 is a 68-year old male with T2DM on glimepiride and received canagliflozin 200 mg daily. At Week 24 visit, ALT was elevated at 296 U/L, AST was elevated at 105 U/L, total bilirubin was 0.7 mg/dL, and alkaline phosphatase was 481 U/L. Intrahepatic duct dilation was suspected by abdominal echography. Subject was diagnosed with autoimmune

hepatitis based on serologic testing (elevated IgG4), CT findings such as narrowing of pancreatic duct, retroperitoneal fibrosis and interstitial nephritis.

Dr. Seeff agreed with the diagnosis provided by the applicant for these two cases, based on the limited available information.

Please refer to Dr. Seeff's review of the hepatic events for complete details.

At the 4-Month Safety Update, four additional cases that met the Biochemical Hy's law were identified, one with placebo, one with glimepiride, and two with canagliflozin (one each of 100 mg and 300 mg). Both cases with canagliflozin (subject 100516 and (b) (4) were diagnosed with cholecystitis.

3.10 Genital Infections

An increase in urinary glucose excretion caused by canagliflozin treatment has the potential to increase fungal growth in the perineum and genitourinary tract. Perineal and genito-urinary tract mycotic infections were considered adverse event of special interest in this program. The results of male and female genital infections included all events regardless of glycemic rescue therapy as glycemic rescue therapy is not expected to affect these adverse events.

The Placebo-Controlled Studies Dataset (DS1) was used as the primary population to characterize genital infections. In addition, results from individual trial DIA3010 and DIA3008 are further discussed since DIA3010 included older population and subjects in DIA3008 have different baseline characteristics compared to DS1 as discussed previously. There were very few mycotic infections in DIA3004 (subjects with moderate renal impairment), as one woman and two men reported genital mycotic infection.

<u>Female Genital Mycotic Infections</u>

Two groups of search terms were used to capture genital mycotic infections in females:

- Specific List of vulvovaginal adverse events included the following terms: Genital candidiasis, Genital infection fungal, Urogenital infection fungal, Vaginal infection, Vaginal inflammation, Vulvitis, Vulvovaginal candidiasis, Vulvovaginal mycotic infection, and Vulvovaginitis.
- Broad list of vulvovaginal adverse events included the terms in specific list above *plus* following additional terms with signs or symptoms potentially consistent with mycotic vulvovaginitis AEs: Genital burning sensation, Genital discharge, Genital discomfort, Pruritus genital, Vaginal discharge, Vaginal erosion, Vaginal exfoliation, Vaginal hemorrhage, Vaginal lesion, Vaginal odor, Vaginal swelling, Vulval disorder, Vulval edema, Vulvovaginal burning sensation, Vulvovaginal discomfort, Vulvovaginal disorder, Vulvovaginal dryness, Vulvovaginal erythema, Vulvovaginal pain, Vulvovaginal pruritis, Vulvovaginal ulceration.

The broad list contain some non-specific term that may not indicate a genital mycotic infection (e.g., vulvovaginal pain, vulvovaginal dryness).

The incidence of female genital mycotic infections in DS1, DIA3010, and DIA3008 are summarized in Table 42. In the Placebo-Controlled Studies Dataset (DS1), the incidence of female genital mycotic infections were higher in both canagliflozin treatment groups (12.9% and 14.9% in 100 mg and 300 mg group respectively) compared to placebo (3.2%) without dose-dependency. The incidence using the 'specific' list show similar trend as the 'broad' list. The most commonly reported adverse event terms were vulvovaginal mycotic infection and vulvovaginal candidiasis.

In DS1, women who experienced vulvovaginitis (specific list) compared to women who did not experience vulvovaginitis were slightly younger (mean age of 53.8 years compared to 55.8 years), more likely to be pre-menopausal (36% versus 27%), had a previous history of vulvovaginitis (29% versus 12%), and more likely to be living in North America (60% compared to 42%).

DIA3010 included older subjects with T2DM with a median age of 63 years (57 years in DS1) and greater median duration of diabetes (10 years compared to 6 years in DS1). The proportion of women who were post-menopausal was also higher in DIA3010 (97%) compared to DS1 (73%). The incidence of female genital mycotic infections was higher in both canagliflozin groups compared to placebo in DIA3010, and higher in the canagliflozin 100 mg group (15.4%) compared to 300 mg group (11.2%) as shown in Table 42.

Similar to DS1, a higher incidence of female genital mycotic infections was seen in DIA3008 with canagliflozin compared to placebo without dose-dependency. Compared to DS1, DIA3008 trial included older T2DM subjects with longer duration of T2DM, multiple comorbidities, diabetic complications, and had lower eGFR at baseline. The proportion of women who were post-menopausal was higher in DIA3008 (93%) compared to DS1 (73%).

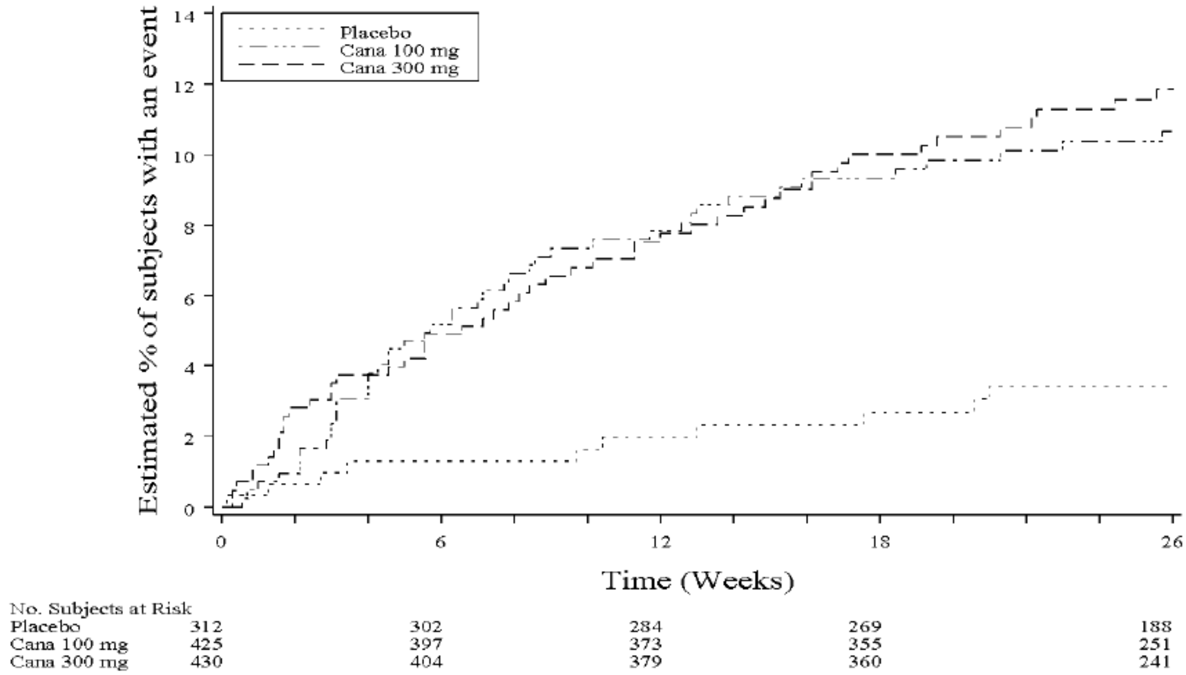
Table 42: Summary of Female Genital Mycotic Infections - Regardless of Rescue

	Placebo	Cana 100 mg	Cana 300 mg	All Cana
DS1	N=312	N=425	N=430	N=855
Vulvuovaginal AEs (broad), n (%)	10 (3.2)	55 (12.9)	64 (14.9)	119 (13.9)
Incidence rate per subject-year	0.07	0.28	0.32	0.30
Vulvovaginal AEs (specific), n (%)	10 (3.2)	44 (10.4)	49 (11.4)	93 (10.3)
Incidence rate per subject-year	0.07	0.22	0.25	0.23
Subjects with >1 event, n (%)	1 (0.3)	10 (2.4)	10 (2.3)	20 (2.3)
DIA3010	N=94	N=117	N=107	N=224
Vulvuovaginal AEs (specific), n (%)	2 (2.1)	18 (15.4)	12 (11.2)	30 (13.4)
DIA3008	N=486	N=484	N=497	N=981
Vulvovaginal AEs (specific), n (%)	11 (2.3)	72 (14.9)	65 (13.1)	137 (14.0)

Source: ISS, Table 86, 87, 90, 91

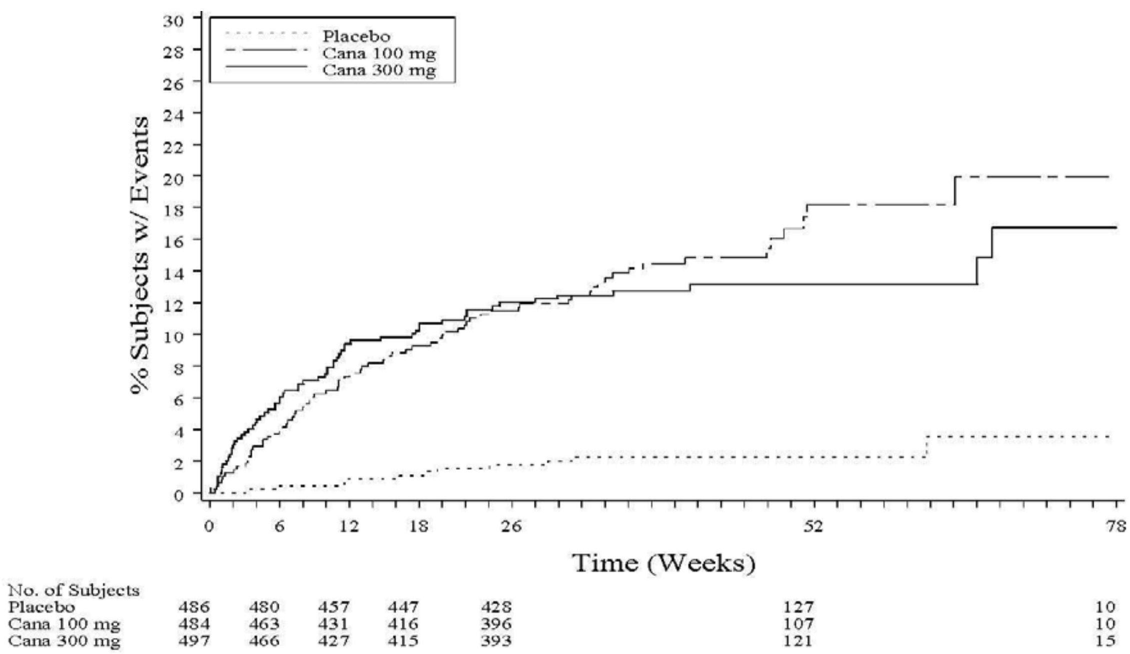
The Kaplan-Meier curve for female genital mycotic infections in DS1, as shown in Figure 6, showed a linear increase in the incidence of female genital mycotic infections in both canagliflozin groups without a plateau at the end of Week 26. However, in the Kaplan-Meier curve for DIA3008 (Figure 7), which contained longer duration of follow-up compared to DS1, the curve appear to plateau after 26 weeks.

Figure 6: Kaplan-Meier Plot of Time to First Mycotic Vulvovaginitis (Specific) in DS1



Source: ISS, Figure 1

Figure 7: Kaplan-Meier Plot of Time to Female Mycotic Infections (Specific) in DIA3008



In DS1, the mean duration of genital mycotic infections in women was not significantly different between treatment groups (19 days and 20 days for combined canagliflozin and placebo groups respectively). The mean duration of symptoms was slightly longer in the combined canagliflozin

treatment group (11 days) compared to placebo (9 days). Among women with genital mycotic infection, more women in the combined canagliflozin group had more than one event (23% [20/93]) compared to placebo (10% [1/10]).

No vulvovaginitis events were serious in DS1, DIA3010, and DIA3008. In DS1, six subjects discontinued due to vulvovaginitis in the combined canagliflozin group (four and two in 100 mg and 300 mg respectively) compared to none in the placebo group. In DIA3010, two women discontinued and one woman temporarily interrupted study drug due to genital mycotic infection; all three were receiving canagliflozin 300 mg. In DIA3008, six women in canagliflozin 100 mg and 11 women in canagliflozin 300 mg group discontinued due to genital mycotinc infecion, compared to none in the placebo group.

Male Genital Mycotic Infections

The following search terms were used to identify adverse events of male genital mycotic infections: Balanitis, Balanitis candida, Balanoposthitis, Balanoposthitis infective, Erosive balanitis, Gangrenous balanitis, Genital candidiasis, Genital infection, Genital infection fungal, Penile candida, Penile infection, and Posthitis.

The incidence of male genital mycotic infections in DS1, DIA3010, and DIA3008 are summarized in Table 43. In DS1, the overall incidence of genital mycotic infections in males was low compared to females, and the incidence of male genital mycotic infections was higher in two canagliflozin groups (4.2% and 3.7% with 100 mg and 300 mg respectively) compared to placebo (0.6%) without dose-dependency.

Table 43: Summary of Male Genital Mycotic Infections - Regardless of Rescue

	Placebo	Cana 100 mg	Cana 300 mg	All Cana
DS1	N=334	N=408	N=404	N=812
Male Genital Infections AEs, n (%)	2 (0.6)	17 (4.2)	15 (3.7)	32 (3.9)
Incidence rate per subject-year	0.01	0.09	0.09	0.08
Subjects with >1 event, n (%)	0	2 (0.5)	5 (1.2)	7 (0.9)
DIA3010	N=143	N=124	N=129	N=253
Male Genital Infections AEs, n (%)	0	4 (3.2)	8 (6.2)	12 (4.7)
DIA3008	N=995	N=961	N=944	N=1905
Male Genital Infections AEs, n (%)	13 (1.4)	65 (6.8)	96 (10.2)	161 (8.5)

Source: ISS, Table 93, 96, 97

In DS1, the following baseline characteristics were notable when you compare baseline characteristics between men who did and did not have an adverse event of genital mycotic infection in the combined canagliflozin group:

- Male genital mycotic infections were more commonly reported in men who were uncircumcised; among 31 men with known circumcision status in the combined canagliflozin treatment group, myotic infections occurred in 0.7% (2/291) of circumcised men compared to 5.7% (29/506) uncircumcised men;
- A larger number of men had a prior history of balanitis/balanoposthitis in men who had genital mycotic infections (25%) compared to men who did not have genital mycotic infections (2%) in the combined canagliflozin group;
- The mean duration of diabetes was slightly longer in men with mycotic infections (9.3 years) compared to those without mycotic infections (7.2 years);

- Male genital mycotic infections occurred more in Europe compared to North America (44% and 25% respectively), but this may be partly be due to the lower prevalence of circumcision in Europe compared to North America (62% and 4% of men respectively).

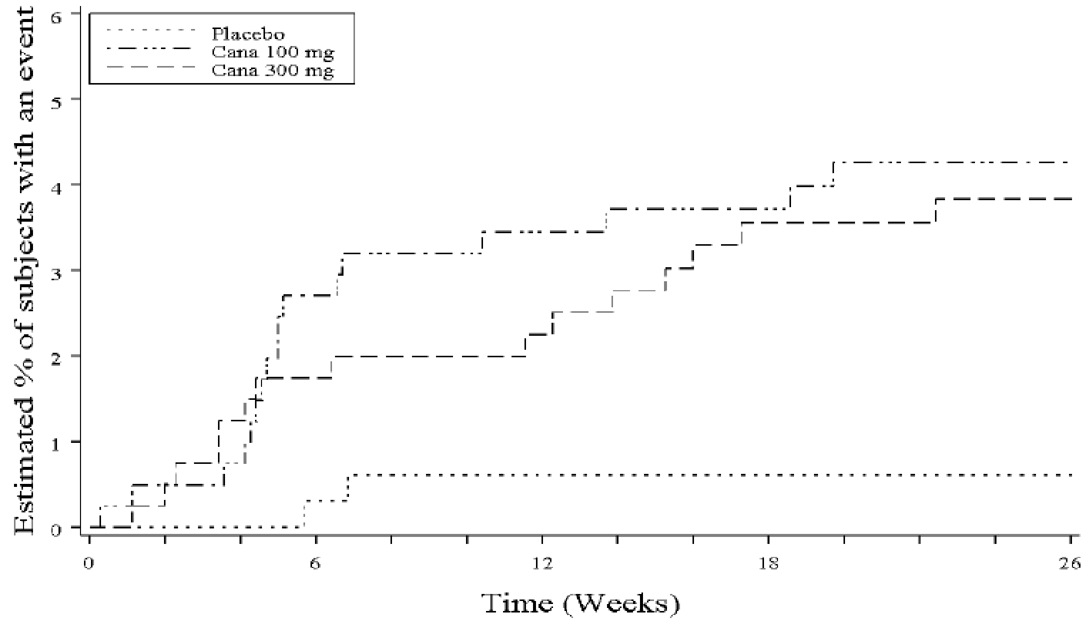
In DIA3010, all male genital infections occurred in the canagliflozin groups, and a higher incidence was observed with canagliflozin 300 mg (6.2%) compared to 100 mg (3.2%) showing dose-dependency. Subjects in DIA3010 were older, less males were uncircumcised (53% compared to 62% in DS1), and had similar history of balanitis or balanoposthitis. Of 12 subjects with male genital infections in the combined canagliflozin group, 10 subjects (85%) were uncircumcised. None had a previous history of balanitis or balanoposthitis.

The incidence of male genital infections was higher in DIA3008 compared to DS1 or DIA3010, with a higher incidence with canagliflozin 300 mg (10.2%) compared to 100 mg (6.8%) showing dose-dependency. The higher incidence of male genital infections in DIA3008 compared to DS1 may be related to the fact that more male subjects in DIA3008 were uncircumcised (72% versus 62%) and had a history of balanitis or balanoposthitis (5% versus 3%) compared to DS1. As previously noted, subjects in DIA3008 were also older, had a longer duration of diabetes, with a lower eGFR at baseline, and the mean duration of exposure to study drug in DIA3008 at interim analysis was almost twice as long as DS1.

In DS1, the mean duration of male genital mycotic infections were longer in the combined canagliflozin group (40 days) compared to the placebo group (mean and median of 16 days). In addition, the mean duration of symptoms after initiation of treatment was also longer in the combined canagliflozin group (23 days) compared to the placebo group (13 days). Among men with genital mycotic infection, a higher proportion of men in canagliflozin 300 mg group (33% [5/15]) had two or more events of genital mycotic infections compared to 100 mg group (12% [2/17]), whereas no subjects in placebo had more than one event.

As shown in Figure 8, the increase in the incidence of male genital infections with canagliflozin was apparent early in DS1, and most events occurred by Week 18. In DIA3008, as shown in Figure 9, the proportion of male subjects with genital mycotic infections appear to increase linearly without plateau, at least until Week 52; since this is an interim analysis, not much data is available past Week 52.

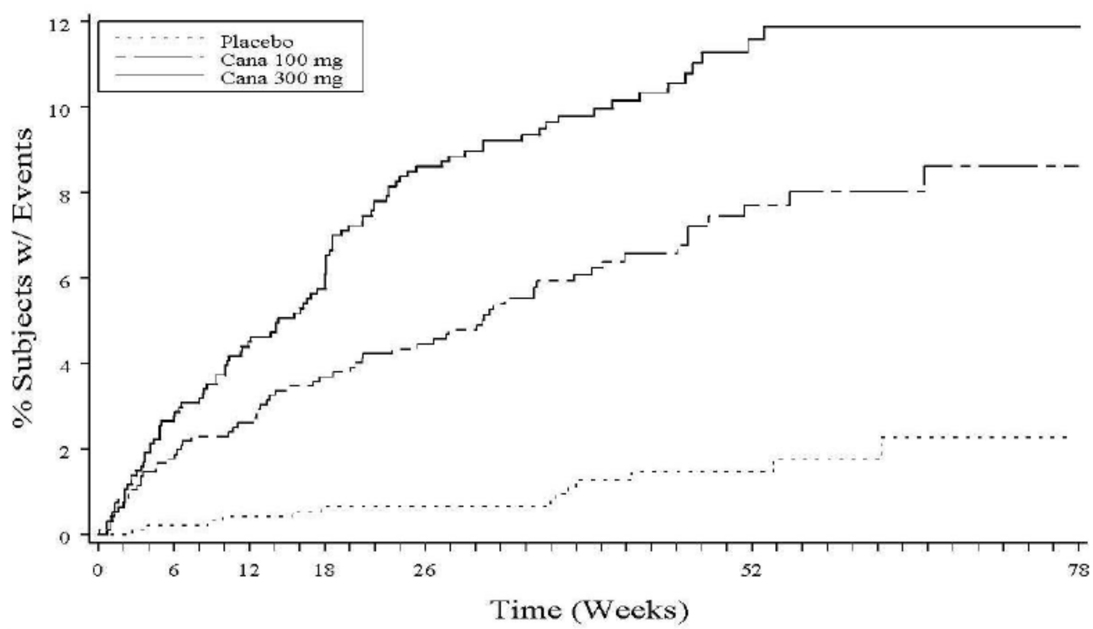
Figure 8: Kaplan-Meier Plot of Time to the First Male Genital Infections - DS1



No. Subjects at Risk					
Placebo	334	332	320	304	200
Cana 100 mg	408	395	371	355	259
Cana 300 mg	404	394	377	357	263

Source: ISS, Figure 4

Figure 9: Kaplan-Meier Plot of Time to First Male Genital Infections - DIA3008 Interim Analysis



No. of Subjects							
Placebo	955	950	914	876	858	340	49
Cana 100 mg	961	939	913	888	866	341	56
Cana 300 mg	944	909	856	830	784	299	44

Source: Figure 5

None of the male genital mycotic infections in DS1, DIA3010, and DIA3008 were serious event. In DS1, four men in the canagliflozin group (2 in each 100 mg and 300 mg groups) compared to none in placebo group discontinued due to male genital mycotic infection. In DIA3010, one subject discontinued due to male genital mycotic infection. In DIA3008, three male subjects (0.3%) and eight male subjects (0.8%) with canagliflozin 100 mg and 300 mg respectively discontinued due to genital mycotic infections, compared to none with placebo.

In DIA3008, in addition to male genital mycotic infections, 9 (0.3%) subjects in the combined canagliflozin group (4 and 5 subjects in 100 mg and 300 mg group respectively) reported adverse event of phimosis or acquired phimosis, compared to none in the placebo group. Four of nine events of phimosis or acquired phimosis were serious. In addition, one subject who received canagliflozin 100 mg reported an adverse event of circumcision. Phimosis, acquired phimosis, and circumcision were only reported in DIA3008 and not reported during the core periods in any other Phase 3 trials.

3.11 Urinary Tract Infections

Increases in urinary glucose excretion caused by canagliflozin could also potentially increase bacterial growth in the genito-urinary tract and lead to increased incidence of urinary tract infections (UTI). The results of UTI included all events regardless of glycemic rescue therapy since glycemic rescue therapy have not been associated with UTIs.

The MedDRA Preferred Terms for UTIs included a wider list of terms consistent with a diagnosis of UTI (i.e., cystitis, pyelonephritis, etc) to identify all UTI events, and a list of Preferred Terms consistent with upper UTIs (i.e., pyelonephritis, urosepsis, etc) were used to identify upper UTIs.

In addition, a supplemental eCRF was used to capture information related to UTIs, and to categorize all UTIs as:

- Symptomatic UTIs
- Asymptomatic UTIs
- Symptomatic UTIs confirmed by laboratory testing
- Upper UTIs based on a list of specific search terms (Bacterial pyelonephritis, Emphysematous pyelonephritis, Kidney infection, Pyelonephritis fungal, Pyonephrosis, Renal abscess, Perinephric abscess, Pyelonephritis, Pyelonephritis acute, Pyelonephritis chronic, Pyelocystitis, Pyelonephrosis, Renal cyst infection, and Urosepsis)

The UTI events were evaluated in the Placebo-controlled Studies Dataset (DS1) to characterize these events, and the incidence of UTIs were also evaluated in the Moderate Renal Impairment Dataset (DS2) and DIA3010 (older T2DM subjects) since they included subjects who may be more affected by UTI events. DIA3008 was also evaluated to assess UTI events over a longer treatment duration.

The incidences of UTI for DS1, DS2, DIA3010, and DIA3008 are presented in Table 44. In DS1, the incidence of UTI was slightly higher in the canagliflozin 100 mg group (5.9%) compare to canagliflozin 300 mg (4.3%) or placebo group (4.0%).

Table 44: Summary of Urinary Tract Infections - Regardless of Rescue

	Placebo	Cana 100 mg	Cana 300 mg	All Cana
DS1	N=646	N=833	N=834	N=1667
Subjects with any UTI, n (%)	26 (4.0)	49 (5.9)	36 (4.3)	85 (5.1)
Incidence rate of any UTI per subject-year	0.09	0.13	0.09	0.11
Subjects with symptomatic UTIs, n (%)	17 (2.6)	32 (3.8)	27 (3.2)	59 (3.5)
Subjects with upper UTIs, n (%)	0	1 (0.1)	1 (0.1)	2 (0.1)
DS2	N=382	N=338	N=365	N=703
Subjects with any UTI, n (%)	23 (6.0)	21 (6.2)	27 (7.4)	48 (6.8)
Incidence rate per subject-year	0.09	0.09	0.10	0.10
DIA3010	N=237	N=241	N=236	N=477
Subjects with any UTI, n (%)	12 (5.1)	14 (5.8)	19 (8.1)	33 (6.9)
DIA3008	N=1441	N=1445	N=1441	N=2886
Subjects with any UTI, n (%)	63 (4.4)	72 (5.0)	82 (5.7)	154 (5.3)
Subjects with symptomatic UTIs, n (%)	45 (3.1)	59 (4.1)	60 (4.2)	119 (4.1)

Source: ISS, Table 100, 101, 102, 105, 109, 110

In **the Placebo-controlled Studies Dataset (DS1)**, the majority UTIs occurred in women (87%). The majority of subjects experienced symptomatic UTIs, with a slightly higher proportion of subject in the canagliflozin 300 mg having symptomatic UTIs (75% [27/36]) compared to canagliflozin 100 mg or placebo group (both 65%). The most commonly reported symptoms were dysuria, frequency, urgency, and/or suprapubic pain, reported in >90% of symptomatic events. Two subjects in the canagliflozin groups (an adverse event of kidney infection and urosepsis) and no subject in the placebo group had upper UTIs based on the search of MedDRA terms indicating upper UTIs.

The median time to first symptomatic UTI was earlier with canagliflozin (71 days and 76 days in 100 mg and 300 mg group) compared to placebo (90 days). The median duration of symptomatic UTIs was similar across treatment groups (about 11 to 12 days). Very few subjects had more than one symptomatic UTI with no discernible difference between treatment groups (0.5% [3/646], 0.6% [5/833], and 0.2% [2/834] in placebo, canagliflozin 100 mg, and canagliflozin 300 mg groups respectively).

Three UTI events were severe and all three were also serious UTIs (two subjects and one subject in canagliflozin 100 mg and 300 mg group respectively) in DS1. No other serious UTIs were reported. Also, one subject in the canagliflozin 100 mg group and one subject in the placebo group discontinued due to UTI in DS1.

The incidence of UTI in subjects in **the Moderate Renal Impairment Dataset (DS2)** was higher with canagliflozin 300 mg (7.4%) compared to canagliflozin 100 mg (6.2%) or placebo (6.0%). Three subjects in placebo and one subject in canagliflozin 100 mg reported serious UTI events. Two subjects in placebo and one subject in canagliflozin 100 mg discontinued due to UTI. No UTIs in canagliflozin 300 mg group were serious or led to discontinuation. One

subject in each treatment groups had upper UTI based on the search of MedDRA terms indicative of upper UTIs; only one adverse event of urosepsis in placebo group was serious.

The median time to first symptomatic UTI was earlier with canagliflozin 100 mg (44 days) compared to canagliflozin 300 mg (81 days) or placebo (116 days). The median duration of symptomatic UTIs was similar across treatment groups (11 days with canagliflozin and 13 days with placebo). Similar to DS1, there was no increase in the number of subjects with more than one UTI event with canagliflozin.

The subjects in **DIA3010** were slightly older (median age of 63 years compared to 57 years), longer mean duration of diabetes (10 years versus 6 years), and lower median eGFR (76 mL/min/1.73m^2 versus 86 mL/min/1.73m^2) compared to DS1. Similar to DS2, there was an increase in the incidence of UTIs with canagliflozin 300 mg (8.1%) compared to canagliflozin 100 mg (5.8%) or placebo (5.1%) in DIA3010. Two events of upper UTIs occurred with placebo. No subjects in the canagliflozin groups and three subjects in the placebo group had serious UTI events. Two subjects from canagliflozin group and two subjects from placebo group discontinued due to UTI.

The subjects in **DIA3008** were also slightly older (median age of 63 years), with longer mean duration of diabetes (12 years) and a lower median eGFR (76 mL/min/1.73m^2) at baseline, with a longer duration of exposure compared to DS1. In this trial, there was a higher incidence of UTIs with both canagliflozin groups (5.7% and 5% in 300 mg and 100 mg group respectively) compared to placebo (4.4%). The incidence of upper UTIs was slightly higher with canagliflozin 100 mg (0.6% [9/1445]) compared to canagliflozin 300 mg (0.2% [3/1441]) and placebo (0.3% [5/1441]). The incidence of UTI events that were serious or that led to discontinuation was low across treatment groups and not significantly higher with canagliflozin compared to placebo. Serious UTI events were reported in 3 (0.2%) subjects with both canagliflozin 100 mg and 300 mg compared to 2 (0.1%) subjects with placebo; UTIs leading to discontinuation were reported in 4 (0.3%) and 2 (0.1%) subjects with canagliflozin 100 mg and 300 mg respectively compared to 1 (0.1%) subject with placebo.

3.12 Increase in Low-Density Lipoprotein-Cholesterol (LDL-C)

Treatment with canagliflozin dose-dependently increased LDL-C levels across Phase 3 trials.

In all the Phase 3 trials, blood samples for assessment of fasting plasma lipids were obtained from subjects at baseline (Day 1), and in most studies at the end of the core period, which was either Week 18 (in DIA3008), Week 52 (DIA3009), or Week 26 (for all other Phase 3 trials). The results of DIA3015 are not presented in this section since it is a 52-week active-controlled trial that did not include 100 mg group, but the increase in LDL-C with canagliflozin 300 mg in this trial was consistent with findings in other Phase 3 trials. The LDL-C values were calculated using the Friedewald calculation (based on triglyceride, total cholesterol, and HDL-C) across the Phase 3 program.

<u>Fasting Lipid Changes By Phase 3 Trial</u>

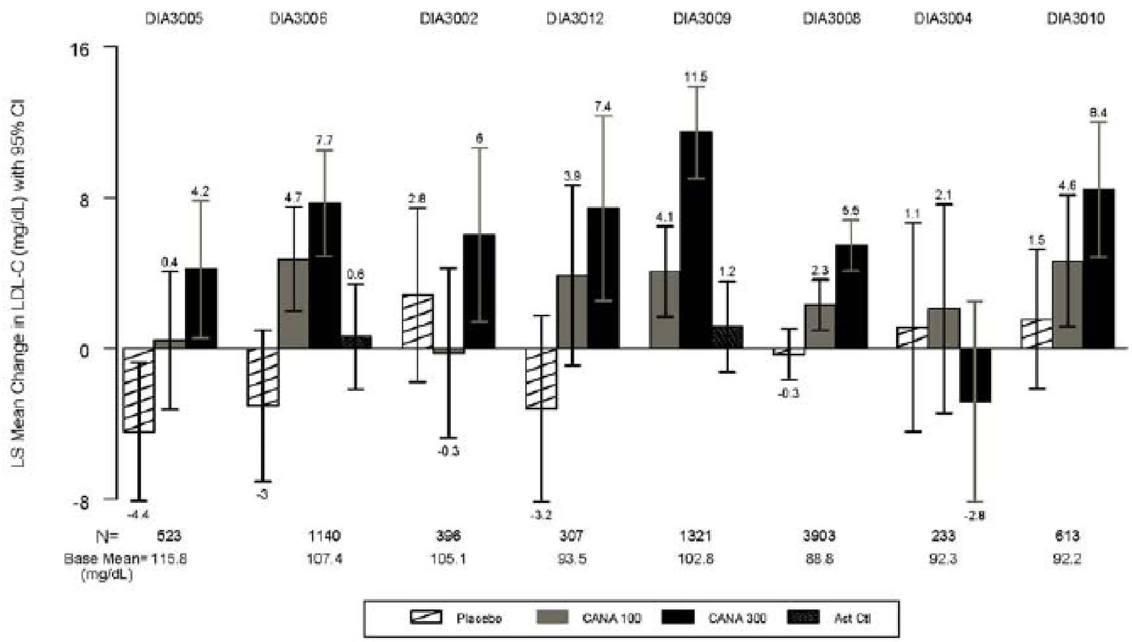
The change in the least squares (LS) mean in LDL-C from baseline to the end of core period for eight Phase 3 trials are summarized in Table 45. The LS mean absolute changes in LDL-C from baseline are shown by treatment group for each Phase 3 trial in Figure 10, and the placebo- or active-control subtracted LS mean absolute change in LDL-C are shown in Figure 11. Unlike other trials which showed a dose-dependent increase in LDL-C levels with canagliflozin, there was a decrease in the LS mean absolute change in LDL-C from baseline with canagliflozin 300 mg in DIA3004 (-3.9 mg/dL); DIA3004 was a smaller trial in subjects with moderate renal impairment. The canagliflozin 100 mg group in DIA3002 also showed a decrease in LS mean absolute change in LDL-C from baseline (-3.1 mg/dL). The largest placebo-subtracted increase in LS mean absolute change in LDL-C from baseline with canagliflozin occurred in DIA3006 and DIA3012.

Table 45: Summary of LS Mean Absolute Change in LDL-C (mg/dL) from Baseline at the End of Core Period By Phase 3 Trial - LOCF, Regardless of Rescue

	Placebo	Cana 100 mg	Cana 300 mg	Active*
DIA3002, N	130	136	130	
Baseline, mean (SD)	111.1 (37.4)	104.0 (42.1)	100.3 (35.0)	
LS mean change from baseline (SE)	2.8 (2.3)	-0.3 (2.3)	6.0 (2.3)	
Placebo-subtracted LS mean (SE) [95% CI]		-3.1 (3.3) (-9.5;3.4)	3.2 (3.3) (-3.3;9.7)	
DIA3005, N	173	174	176	
Baseline, mean (SD)	120.0 (43.7)	117.3 (37.0)	110.2 (35.1)	
LS mean change from baseline (SE)	-4.4 (1.9)	0.4 (1.9)	4.2 (1.9)	
Placebo-subtracted LS mean (SE) [95% CI]		4.8 (2.6) [-0.3;10.1]	8.6 (2.6) [3.4;13.8]	
DIA3006, N	159	330	323	328
Baseline, mean (SD)	104.3 (34.6)	106.7 (31.6)	107.2 (34.8)	109.8 (34.5)
LS mean change from baseline (SE)	-3.0 (2.0)	4.7 (1.4)	7.7 (1.4)	0.6 (1.4)
Placebo-subtracted LS mean (SE) [95% CI]		7.8 (2.5) [2.9;12.7]	10.8 (2.5) [5.9;15.6]	
DIA3012, N	100	106	101	
Baseline, mean (SD)	97.8 (34.9)	92.4 (33.6)	90.3 (31.2)	
LS mean change from baseline (SE)	-3.2 (2.5)	3.9 (2.4)	7.4 (2.5)	
Placebo-subtracted LS mean (SE) [95% CI]		7.1 (3.5) [0.2;13.9]	10.6 (3.5) [3.6;17.6]	
DIA3004, N	76	75	82	
Baseline, mean (SD)	98.4 (38.9)	91.6 (33.9)	87.3 (34.4)	
LS mean change from baseline (SE)	1.1 (2.8)	2.1 (2.8)	-2.8 (2.7)	
Placebo-subtracted LS mean (SE) [95% CI]		1.0 (4.0) [-6.8;8.8]	-3.9 (3.9) [-11.6;3.8]	
DIA3008, N	1293	1323	1287	
Baseline, mean (SD)	89.2 (35.0)	87.9 (35.5)	89.2 (35.8)	
LS mean change from baseline (SE)	-0.3 (0.7)	2.3 (0.7)	5.5 (0.7)	
Placebo-subtracted LS mean (SE) [95% CI]		2.6 (1.0) [0.7;4.5]	5.8 (1.0) [3.9;7.7]	
DIA3009, N		447	433	441
Baseline, mean (SD)		99.7 (35.3)	106.1 (35.9)	102.6 (33.7)
LS mean change from baseline (SE)		4.1 (1.2)	11.5 (1.2)	1.2 (1.2)
Difference of LS mean (SE) minus Glimepiride [95% CI]		2.9 (1.7) [-0.5;6.3]	10.4 (1.7) [7.0;13.8]	
DIA3010, N	192	215	206	
Baseline, mean (SD)	91.2 (35.0)	93.8 (38.3)	90.7 (33.4)	
LS mean change from baseline (SE)	1.5 (1.9)	4.6 (1.8)	8.4 (1.8)	
Placebo-subtracted LS mean (SE) [95% CI]		3.1 (2.6) [-2.0;8.2]	6.9 (2.6) [1.7;12.0]	

*Sitagliptin in DIA3006; Glimepiride in DIA3009
Note: End of core period is Week 52 in DIA3009, Week 18 in DIA3008, and Week 26 for all other studies.
Source: ISS, DLIP01A_ALL_CNV

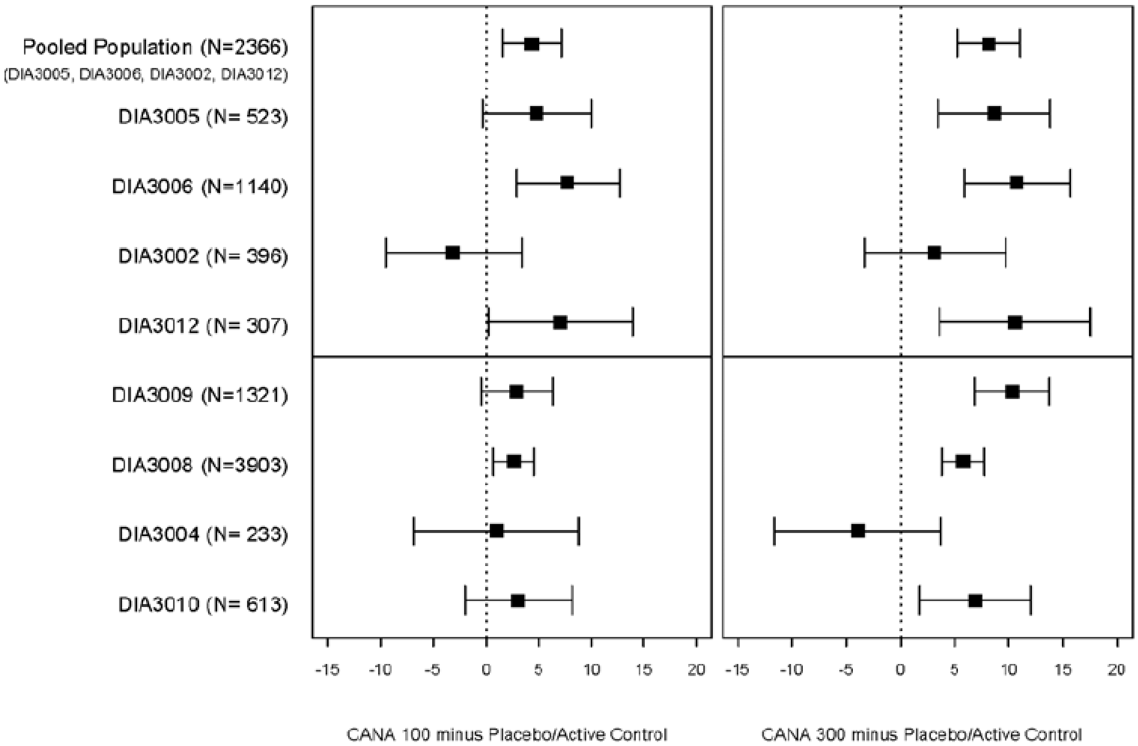
Figure 10: LS Mean Absolute Change in LCL-C (mg/dL) from Baseline at the End of Core Period By Phase 3 Trial - LOCF, Regardless of Rescue



Note: LS Mean and 95% CI are derived via ANCOVA model including treatment and baseline value. Numbers in graph represent the LS mean.

NOTE: DIA3009 only had an active control (glimepiride). DIA3006 had placebo and active control (sitagliptin).
Source: ISS, Figure 31

Figure 11: Placebo- or Active-Control Subtracted LS Mean Absolute Change in LDL-C (mg/dL) from Baseline at the End of Core Period By Phase 3 Trial

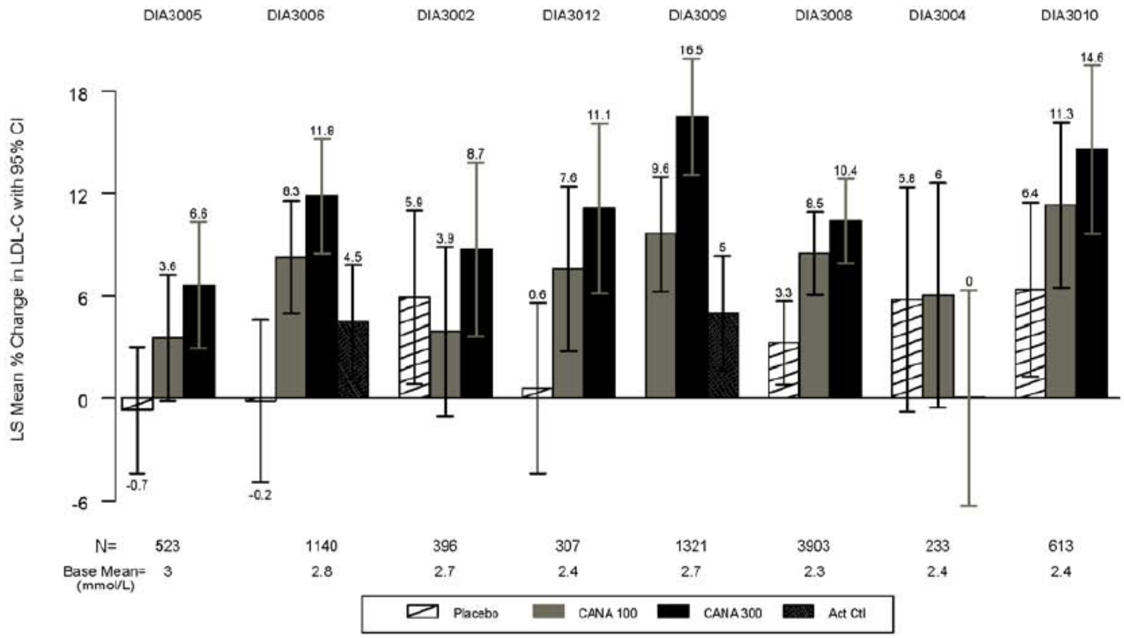


Note: LS Mean diff and 95% CI is between Cana and Glimepiride for DIA3009, is between Cana and Placebo for the rest studies.
Pooled Population includes Study DIA3005, DIA3006, DIA3002, DIA3012.

Source: ISS, Figure 33

The LS mean percent changes in LDL-C from baseline at the end of core period for each Phase 3 trial are shown in Figure 12, and placebo- or active-control subtracted LS mean percent changes are shown in Figure 13. The placebo- or active-control subtracted LS mean percent change in LDL-C from baseline ranged from -2% (DIA3002) to 8.5% (DIA3006) for canagliflozin 100 mg and 2.8% (DIA3002) to 12% (DIA3006) for canagliflozin 300 mg.

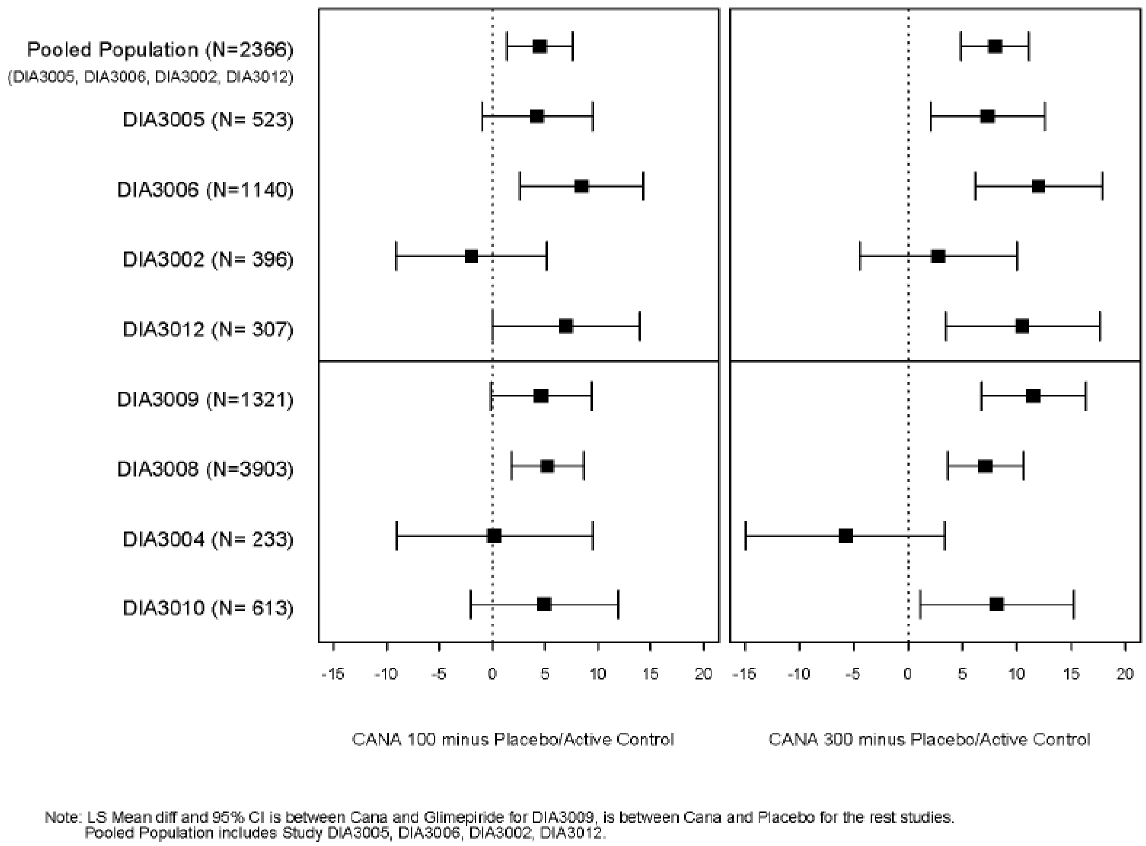
Figure 12: LS Mean % Changes in LDL-C from Baseline at the End of Core Period By Phase 3 Trial



Note: LS Mean and 95% CI are derived via ANCOVA model including treatment and baseline value. Numbers in graph represent the LS mean.

Source: ISS, Figure 34

Figure 13: Placebo- or Active-Control Subtracted LS Mean % Change in LDL-C from Baseline at the End of Core Period By Phase 3 Trial



Source: ISS, Figure 35

The LS mean percent increase in non-HDL-C from baseline at the end of core period was smaller than the changes seen with LDL-C. The placebo- or active-control subtracted LS mean percent change in non-HDL-C from baseline ranged from -1.9% (DIA3002) to 4.1% (DIA3006) with canagliflozin 100 mg. The placebo- or active-control subtracted LS mean percent change in non-HDL-C from baseline ranged from -0.6% (DIA3004) to 5.7% (DIA3010).

The placebo- or active-control subtracted LS mean percent change in LDL-C/HDL-C from baseline at the end of core period ranged from -5.7% (DIA3004) to 2.3% (DIA3012) with canagliflozin 100 mg, and ranged from -9.4% (DIA3004) to 5.5% (DIA3010) with canagliflozin 300 mg.

<u>Lipid Changes in the Placebo-controlled Studies Dataset (DS1)</u>

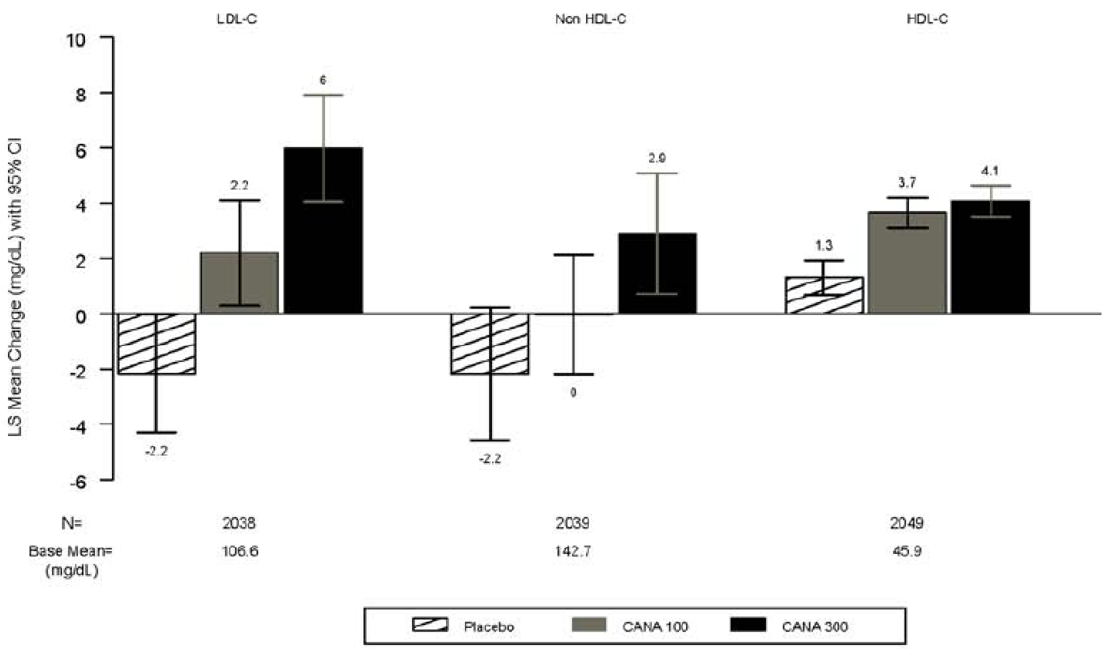
DS1, the pooled dataset of four 26-week controlled trials, was used to examine subgroups that may affect LDL-C response to canagliflozin as this population has similar baseline characteristics.

The use of statin drugs would be an important factor that would affect LDL-C levels, and statin use at baseline and during post-baseline was assessed in DS1. About 41% of subjects in each

treatment group were receiving statin at baseline in DS1. Slightly lower proportion of subjects on canagliflozin 300 mg started or modified their statin dose during the trial (1.6% [13/834]) compared to canagliflozin 100 mg (2.5% [21/833]) or placebo (2.5% [16/646]). It is unlikely that such a small change in statin use during the study period would significantly alter the effects of canagliflozin on lipid levels.

The LS mean absolute changes for LDL-C, non-HDL-C, and HDL-C from baseline for DS1 are presented in Figure 14. There was a dose-dependent increase in the LS mean change in LDL-C from baseline with canagliflozin 100 mg (2 mg/dL) and 300 mg (6 mg/dL), compared to a decrease in LS mean change from baseline with placebo (-2 mg/dL). The placebo-subtracted LS mean change in LDL-C from baseline to Week 26 was 4.4 mg/dL (95% CI:1.5; 7.2) and 8.2 mg/dL (95% CI:5.3;11.0) in canagliflozin 100 mg and 300 mg group respectively. The placebo-subtracted LS mean change in HDL-C from baseline to Week 26 was 2.3 mg/dL (95% CI:1.5; 3.1) and 2.8 mg/dL (95% CI:1.9; 3.6) in canagliflozin 100 mg and 300 mg group respectively. The placebo-subtracted LS mean change in triglycerides from baseline to Week 26 was -9.23 mg/dL (95% CI:-18.4;-0.0) and -19.1 mg/dL (95% CI:-28.3;-9.8) in canagliflozin 100 mg and 300 mg group respectively.

Figure 14: LS Mean Absolute Changes in Fasting Lipids (mg/dL) from Baseline to Week 26 in DS1



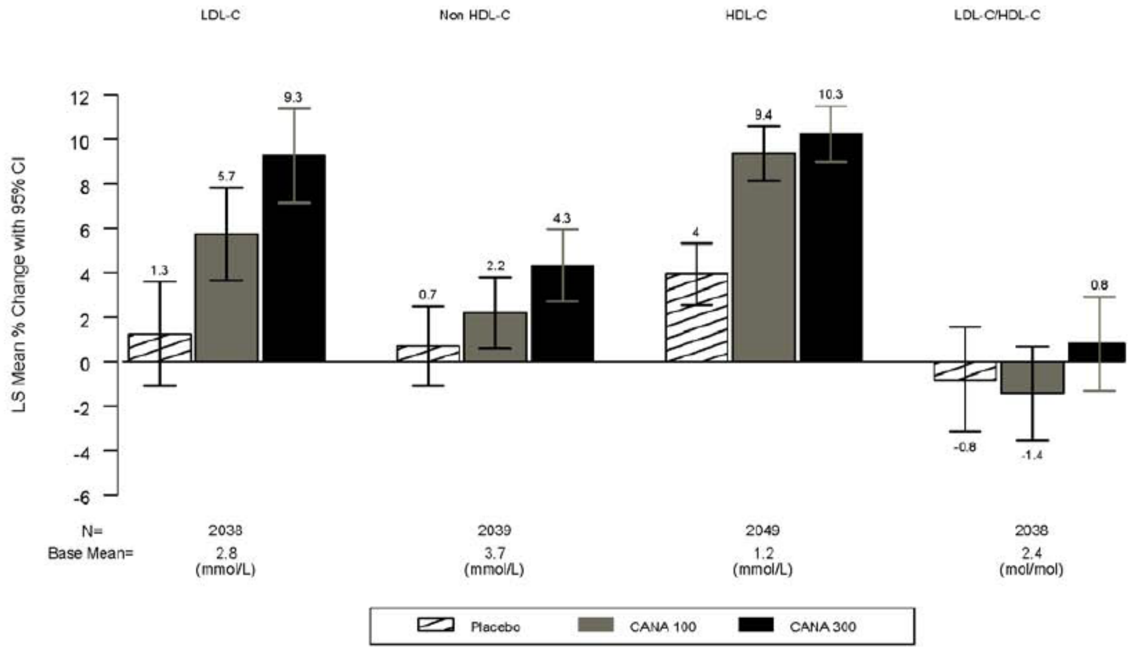
Note: LS Mean and 95% CI are derived via ANCOVA model including treatment, Study ID and baseline value. Numbers in graph represent the LS mean.

Source: ISS, Figure 38

The LS mean percent changes in LDL-C, non-HDL-C, and HDL-C from baseline for DS1 are presented in Figure 15. Corresponding to absolute mean change, there was a dose-dependent increase in the LS mean percent change in LDL-C from baseline at Week 26 with canagliflozin 100 mg (5.7%) and 300 mg (9.3%), compared to placebo (1.3%). The placebo-subtracted LS

mean percent change in LDL-C at Week 26 was 4.5% (95% CI:1.4;7.6) and 8.0% (95% CI:4.9;11.1) with canagliflozin 100 mg and 300 mg respectively. The placebo-subtracted LS mean percent change in HDL-C at Week 26 was 5.4% (95% CI:3.6;7.2) and 6.3% (95% CI:4.5;8.2) with canagliflozin 100 mg and 300 mg respectively. The placebo-subtracted LS mean percent change in triglyerides at Week 26 was -5.2% (95% CI:-10.0;-0.3) and -7.6% (95% CI:-12.5;-2.8) with canagliflozin 100 mg and 300 mg respectively.

Figure 15: LS Mean Percent Change from Baseline at Week 26 in DS1

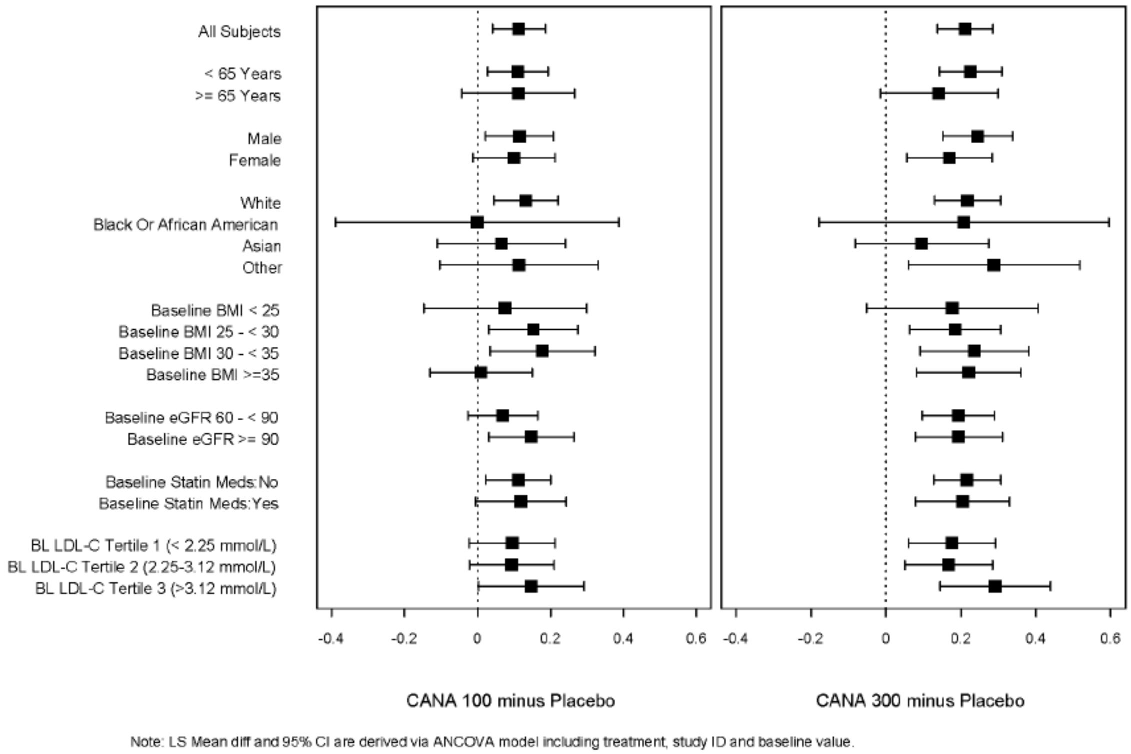


Note: LS Mean and 95% CI are derived via ANCOVA model including treatment, Study ID and baseline value. Numbers in graph represent the LS mean.

Source: ISS, Figure 39

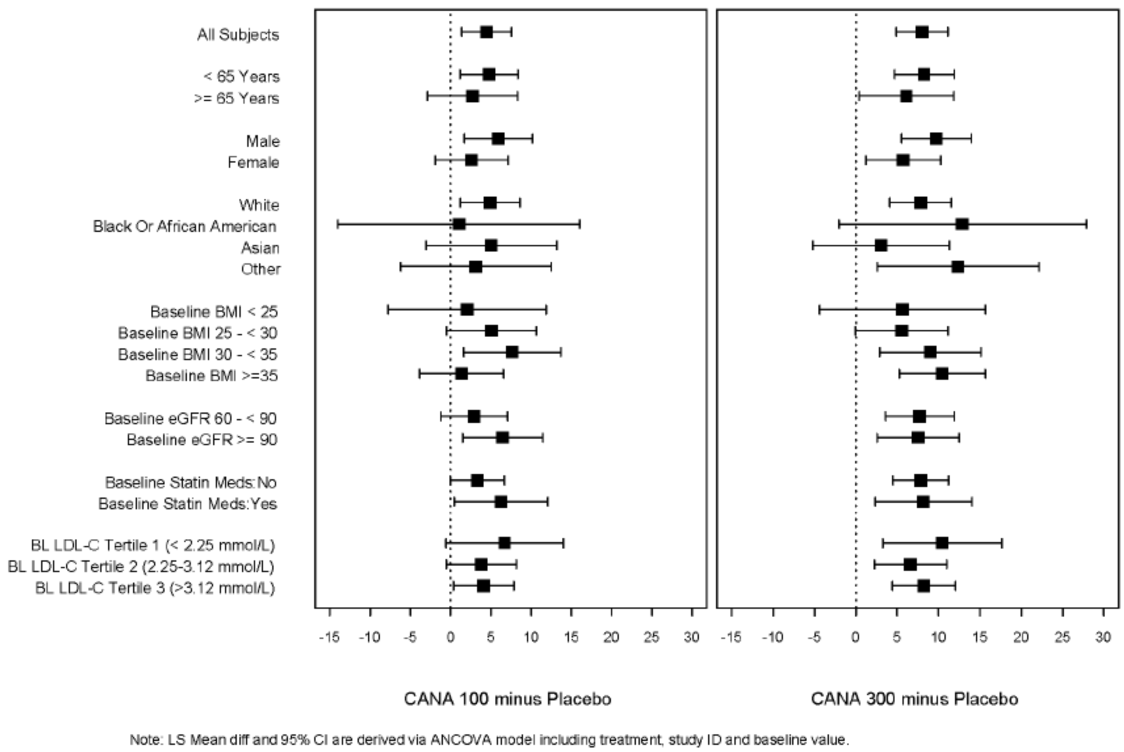
Subgroup analyses were conducted in DS1 in order to assess potential baseline factors that may affect the LDL-C change observed with canagliflozin. The LS mean change in LDL-C in various subgroups based on age, sex, race, BMI, estimated eGFR, baseline statin use, and baseline LDL-C by tertile did not demonstrate any meaningful change in a particular subgroup, as shown in Figure 16. Figure 17 shows the pattern of LS mean percent change in LDL-C in various subgroups in DS1. The nominal p-value for interaction between treatment and each of the subgroup was >0.1.

Figure 16: Placebo-Subtracted LS Mean Absolute Change in LDL-C from Baseline in Subgroups - DS1



Source: ISS, Figure 40

Figure 17: Placebo-Subtracted LS Mean % Change in LDL-C from Baseline in Subgroups - DS1



Source: ISS, Figure 41

The applicant conducted additional analysis of Apo B measurement through a specialty core laboratory (Pacific Biosciences) in archived samples from two trials, DIA3005 and DIA3006. The applicant selected DIA3006 for assessment of Apo B because of relatively large sample size and higher LDL-C increase compared to other trials. DIA3005 was selected by applicant for comparison since the LDL-C changes in this trial was more modest. In addition, LDL-C particle number was obtained using nuclear magnetic resonance (NMR) spectroscopy done by a specialty core lab (Liposciences) for DIA3006.

In DIA3005, the LS mean percent changes in Apo B from baseline to Week 26 were 1.3%, 3.2%, and -0.2% with canagliflozin 100 mg, 300 mg, and placebo respectively, with the placebo-subtracted LS mean percent changes of 1.5% (95% CI:-2.5;5.5) and 3.4% (95% CI:-0.7;7.5) with canagliflozin 100 mg and 300 mg respectively. In DIA3006, the LS mean percent change in Apo B from baseline to Week 26 were 3.9%, 5.1%, and 1.2% with canagliflozin 100 mg, 300 mg, and placebo respectively, with the placebo-subtracted LS mean percent change of 2.6% (95% CI:-1.3;6.6) and 3.8% (95% CI:-0.1;7.8) with canagliflozin 100 mg and 300 mg respectively.

The magnitude of changes from baseline in non-HDL-C in DIA3005 and DIA3006 were similar to the changes reported for Apo B. In DIA3005, the placebo-subtracted mean percent change in non-HDL-C from baseline to Week 26 was 2.0% and 4.0% in canagliflozin 100 mg and 300 mg respectively. In DIA3006, the placebo-subtracted mean percent change in non-HDL-C from baseline to Week 26 was 4.4% and 6.5% in canagliflozin 100 mg and 300 mg respectively.

Table 46 presents the LDL particle assessment by NMR spectroscopy for DIA3006. There was a dose-dependent increase in the total LDL-C particle number with canagliflozin, with placebo-subtracted LS mean percent increase of 3.2% and 5.0% in canagliflozin 100 mg and 300 mg group respectively. These changes in the total LDL-C particle number was smaller than changes for LDL-C; using Friedewald calculation, the placebo-subtracted LS mean percent change was 9.6% and 14.5% in canagliflozin 100 mg and 300 mg respectively. The increase in the total LDL-C particle number was largely driven by an increase in the large LDL-C subfraction in both canagliflozin 100 mg and 300 mg group, with little to small increase in the small LDL-C particle number (Table 46).

Table 46: DIA3006 Total LDL Particle Numbers, % Change from Baseline to Week 26 LOCF, Regardless of Rescue

Analysis Set: Modified Intent-to-Treat

	Placebo (N=183)	Cana 100 mg (N=368)	Cana 300 mg (N=367)
Plasma LDL Particles (nmol/L)			
Value at Baseline			
N	147	291	279
Mean (SD)	1329.3 (409.356)	1382.8 (383.694)	1377.6 (417.938)
Median (Range)	1304.0 (270.0;2645)	1371.0 (461.0;2794)	1342.0 (174.0;2748)
Value at Week 26 LOCF			
N	147	291	279
Mean (SD)	1340.8 (433.676)	1425.9 (434.191)	1442.0 (466.517)
Median (Range)	1265.0 (297.0;2866)	1388.0 (343.0;3126)	1383.0 (207.0;3329)
% Change from Baseline			
N	147	291	279
Mean (SD)	2.9 (21.5)	5.1 (25.2)	7.0 (25.3)
LS Mean (SE)	2.2 (2.0)	5.4 (1.5)	7.2 (1.5)
Median (Range)	0.6 (-51.3;87.1)	2.7 (-70.5;197.7)	5.5 (-68.6;150.2)
Diff. of LS Means (SE)(b)(minus Placebo)		3.2 (2.4)	5.0 (2.4)
95% CI (a)		(-1.4;7.9)	(0.3;9.7)
Plasma Large LDL Particles (nmol/L)			
Value at Baseline			
N	144	285	275
Mean (SD)	286.07 (193.568)	301.05 (213.053)	311.71 (202.809)
Median (Range)	270.00 (8.0;1118)	256.00 (2.0;1378)	274.00 (10.0;934.0)
Value at Week 26 LOCF			
N	144	285	275
Mean (SD)	285.47 (210.006)	333.29 (235.009)	338.87 (227.218)
Median (Range)	243.00 (0.0;953.0)	278.00 (0.0;1133)	297.00 (0.0;1215)
% Change from Baseline			
N	144	285	275
Mean (SD)	20.3 (117.5)	59.0 (324.5)	37.0 (121.8)
LS Mean (SE)	26.6 (19.3)	67.9 (14.1)	48.8 (14.4)
Median (Range)	-4.0 (-100.0;1137.5)	5.3 (-100.0;3600.0)	7.2 (-100.0;1033.3)
Diff. of LS Means (SE)(b)(minus Placebo)		41.4 (22.5)	22.2 (22.7)
95% CI (a)		(-2.9;85.7)	(-22.4;66.8)
Plasma Small LDL Particles (nmol/L)			
Value at Baseline			
N	147	289	277
Mean (SD)	997.88 (424.837)	1041.7 (435.872)	1019.6 (432.691)
Median (Range)	973.00 (39.0;2475)	1029.0 (45.0;2575)	962.00 (56.0;2437)
Value at Week 26 LOCF			
N	147	289	277
Mean (SD)	1001.5 (451.597)	1049.4 (484.523)	1047.6 (479.321)
Median (Range)	968.00 (16.0;2610)	1001.0 (0.0;2614)	998.00 (10.0;2875)
% Change from Baseline			
N	147	289	277
Mean (SD)	10.4 (86.8)	7.1 (52.4)	15.3 (127.3)
LS Mean (SE)	12.5 (8.0)	11.1 (5.8)	18.2 (6.0)
Median (Range)	0.1 (-89.6;948.7)	-0.3 (-100.0;485.2)	2.8 (-98.9;1991.1)
Diff. of LS Means (SE)(b)(minus Placebo)		-1.4 (9.3)	5.7 (9.4)
95% CI (a)		(-19.7;16.9)	(-12.8;24.1)

(a) Pairwise comparison: CIs are based on ANCOVA model with treatment, metformin monotherapy or metformin+SU, and baseline measurement.
(b) Placebo-subtracted change from baseline in LS means
Source: ISS, TAble DEFF27IP_ISS

There is no known mechanism for the LDL-C increase observed with canagliflozin treatment. An increase in LDL-C was not observed with another SGLT2 inhibitor, dapagliflozin, so it is unlikely to be related to SGLT2 inhibition. An increase in LDL-C observed with canagliflozin

have clinical implication, as data from the Cholesterol Treatment Trialists' Collaboration have shown that for each 1 mmol/L (~38.7 mg/dL) LDL cholesterol reduction, the annual major vascular events are reduced by about a fifth, irrespective of baseline cholesterol level.[1] Given that there is a continuous positive linear relationship between CV risk and LDL cholesterol level, a 8.2 mg/dL (~0.2 mmol/L) mean absolute increase in LDL-C observed with canagliflozin 300 mg in DS1 would translate into ~4% increase in the incidence of major vascular events annually.

The cardiovascular meta-analysis conducted by the applicant did not show an increased incidence of major adverse cardiovascular events (MACE, including CV death, nonfatal myocardial infarction, and nonfatal stroke) with canagliflozin, although the 95% confidence interval did cross 1. Please refer to Dr. Eugenio Andraca-Carrera's review of cardiovascular meta-analysis with canagliflozin for further details.

3.13 Discussion of Early Cardiovascular Events in DIA3008

Dr. Andraca-Carrera noted an imbalance in the early cardiovascular (CV) events in the dedicated cardiovascular outcomes trial [DIA3008 (CANVAS)]. During the first 30 days after randomization, 13 CV events occurred on canagliflozin (0.45%) and 1 CV event occurred on placebo (0.07%). DIA3008 enrolled subjects with a high baseline risk for cardiovascular disease. As Dr. Andraca-Carrera describes in his review, the estimated hazard ratio during the first 30 days for DIA3008 was 6.50, with 95% CI not significant due to small number of events (95% CI:0.85,49.66). We compared the baseline characteristics of 13 subjects on canagliflozin with early MACE-plus events to 95 subjects on canagliflozin who had CV events after 30 days to determine if any significant differences in the characteristics of these patients were discernible. We are not providing comparison for placebo with early CV event since there was only one subject.

As shown in Table 47, there were no major differences for the variables considered between subjects receiving canagliflozin who had early CV events compared to those receiving canagliflozin who had CV event after 30 days, or compared to subjects who received placebo and had a CV event in DIA3008.

1 Baigent C, Blackwell L, Emberson J, et al. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. Lancet 2010;376:1670-81.

Table 47: Baseline Characteristics for Canagliflozin Subjects With CV Events, Before and After 30 Days, and Placebo - DIA3008

	Canagliflozin Subjects who had early CV events (N=13)	**Canagliflozin** Subjects with CV event after 30 days (N=95)	**Placebo** All subjects with CV event (N=53)
Baseline Characteristics			
Mean age, yrs	62.3	63.1	64.3
Male	77%	73%	64%
Smoker	31%	18%	13%
Previous CV disease	69%	79%	85%
Caucasian	69%	84%	91%
Baseline LDL, mg/dL	101	101	93
Baseline HbA1c	8.3%	8.2%	8.2%
Baseline BMI	31.1	33.2	32.7
Baseline eGFR	77.3	75.1	73.5
SBP > 140 mmHg*	55%	59%	51%
Statin use	69%	69%	68%

*some missing measurements
Source: Analysis by Dr. Andraca-Carrera

There remains a concern that these early CV events may be related to canagliflozin-induced volume/diuretic changes (i.e., acute kidney injury, hemoconcentration) which occur shortly after initiating canagliflozin.

Two subjects reported low blood pressure at the time of CV event compared to baseline (b) (4)), but at the same time three subjects reported higher blood pressure at the time of CV event compared to baseline (b) (4)). Unfortunately, laboratory values at the time of CV event were not available since these subjects had CV event within 30 days, and the first study visit for assessment was at Week 6. However, no subject reported hypotension or volume depletion-related signs or symptoms concurrent with or before the CV event. In addition, volume depletion events are dose-dependent, and almost equal number of these early CV events occurred in 100 mg and 300 mg groups.

It is also notable that three subjects on canagliflozin who experienced these early CV event ((b) (4) reportedly had signs and symptoms before randomization and initiating study drug.

For one subject ((b) (4) who experienced nonfatal MI, it is possible that nausea, vomiting, and diarrhea, which may have been related to canagliflozin, led to dehydration, diabetic ketoacidosis, and subsequently MI.

Narratives for 14 subjects who had a CV event within 30 days of randomization in DIA3008 are provided here (note that Day 1 is the randomization and first dose of study drug), organized by the CV event, with one placebo case described last:

Cardiovascular Death

Subject (b) (4) ; Treatment Canagliflozin 300 mg

Background AHA therapy: metformin (1500 mg/day), glibenclamide (15 mg/day)
Concomitant medications: From baseline: amlodipine, calcium carbonate, methylcobalamine
Pertinent medical history: T2DM, other diabetic neuropathy, hypertension, tubectomy (1980), nonsmoker

A 54-year old woman complained of headache, giddiness, dizziness, vomiting, and visual disturbance Day before randomization (Day -1). On Day 2, she was hospitalized and received symptomatic treatment, and was diagnosed with vertebrobasilar insufficiency. On exam, she was afebrile with blood pressure (BP) of 150/90 mmgHg and pulse of 116/min (baseline BP was 141/97, pulse 105). She only received one day (Day 1) of study drug. On Day 7, investigator reported that she died due to vertebrobasilar insufficiency. Autopsy was not performed.

Nonfatal Myocardial Infarction (MI)

Subject (b) (4) ; Treatment canagliflozin 300 mg

Background AHA therapy: tolbutamide 1500 mg, metformin 1500 mg
Concomitant medications: From baseline: metoprolol, lisinoprolol, triamterene/epitizude dyta-urese, atorvastatin, acenocoumarol, clopidogrel, carbasalate calcium, paracetamol
Pertinent medical history: March 1993 acute inferior infarction, May 1993 CAG: left dominant system, RCA 99% stenosis, main trunk intact, LAD with mid-trajectory 50% stenosis. RCX is proximally significant; PTCA of the RCX was performed 2004, 2007 and 2009. PTA of the left common iliac artery and left common femoral artery, 2009 fempop on the right. Claudication 2003, endarterectomy arteria femoralis communis 2009, hyperlipidemia 2006, hypertension 2006, MI 1993, PTA A. femoralis communis right 2007, PTA iliac artery left 2004, diabetes 2006, smoker

A 57-year old man with extensive past medical history was hospitalized on Day 6 due to pain high in the back between his shoulders; 12 hours before admission, he experienced continuous pain not responding to sublingual nitroglycerin (used 30x). For the few weeks prior, he was reportedly experiencing episodes of chest pain similar to prior MI. ECG on admission showed sinus rhythm with other normal conduction times, and his serial troponin T levels were elevated at 0.11 and 0.15 ng/mL (normal 0.01 ng/mL), CK-MB levels were normal at 5.9 ug/L (normal 7.6 ug/L), which were elevated during the serial measurements at 11, 47, 43, and 33 ug/L on the same day. A cardiac ultrasound showed left and right ventricles with normal dimensions, good function with RWBS, and no valvular lesions. PCI was performed via PTCA+stent on the LAD; significant stenosis (90%) was present in the LAD at the D1 branch. He was discharged on Day 16 , and continued study until he discontinued for personal reasons; last dose of study drug was Day 186. This subject also experienced muscle pain in both legs on Day 69, and flu on Day 209, both non-serious.

Subject (b) (4) ; Treatment canagliflozin 300 mg

Background AHA therapy: metformin 2000 mg, Rescue medication: glipizide 5 mg
Concomitant medications: From baseline: clopidogrel, metoprolol, acetylsalicylic acid, pravastatin
Pertinent medical history: dyslipidemia 2009, hypertension 2009, myocardial infarction 2009, small vessel coronary artery disease 2009, diabetes 1998, obesity, GERD, smoker

A 37 year old woman was hospitalized for chest pain on Day 12; she developed severe midsternal chest pain radiating to back, arms, and legs without nausea, vomiting, or fever. Her ECG was normal a week before the event. The first set of cardiac enzymes were negative, and she was transferred to another hospital and underwent emergent heart catheterization and PTCA in the distal LAD. Echocardiogram showed mild concentric left ventricular hypertrophy and mild diastolic dysfunction. ECG was normal with 1 to 2 mm of ST elevation in V1 through V4, which was a new finding compared to a year ago. Serial CPK-MB levels on Day 12 were 31, 46.2, and 34.9, with troponin of 9.7, 15.1, and 8.9 (normal <0.5). She was discharged on Day 14. She discontinued the study on Day 470 due to relocation.

Subject (b) (4) ; Treatment canagliflozin 300 mg

Background AHA therapy: metformin (2000 mg/day), glimepiride (4 mg/day)
Concomitant medications: From baseline: irbesartan/hydrochlorothiazide (Karvea HCT), cerivastatin, esomeprazole magnesium, fish oil, fluticasone propionate/salmeterol (Seretide), salbutamol, amlodipine besilate
Pertinent medical history: T2DM, hypertension, asthma, hypercholesterolemia, polymyalgia rheumatica, cataracts, melanoma, removal of melanoma (2008), ex-smoker (ceased 30 years ago)

A 76 year old man presented with sudden chest pain on Day 6 with BP of 138/78 mmHg and pulse 43 (baseline BP was 147/78, and pulse 83). Study drug was discontinued on Day 6 and never restarted. ECG showed complete heart block with ST elevation suggesting acute cardiac ischemia in inferior leads. He reported experiencing right shoulder and neck pain for 10 days. Troponin level drawn in the emergency room was 0.04 ng/mL. He was transferred to another hospital and underwent percutaneous coronary intervention (PCI) for 100% blockage of right coronary artery. Post PCI, he had complete heart block until Day 19 with runs of ventricular tachycardia (last episode on Day 9; received amiodarone on Day 8). On Day 7, his renal and hepatic function deteriorated, which peaked on Day 8 and subsequently improved. Echocardiogram showed normal left and right ventricular with ejection fraction of 60%, mild concentric left ventricular hypertrophy, severe left atrial dilatation and mild right atrial dilatation, and moderate mitral annular calcification with grade ¼ mitral regurgitation. On Day 9, she experienced anemia (hemoglobin 69 g/L; normal 120-180 g/L). The atrioventricular block resolved on Day 10, renal dysfunction resolved on Day 11, anemia resolved on Day 12. Liver dysfunction resolved on Day 18. Subject withdrew from trial on Day 46 for personal reasons.

Subject (b) (4) Treatment Canagliflozin 100 mg

Background AHA therapy: insulin glargine (24 IU/day), insulin aspart (10 IU/day),
Concomitant medications: From baseline: simvastatin, diltiazem, carbamazepine, sulfasalazine, acetylsalicylic acid, nitrazepam, clopidogrel sulfate, cyamposis tetragonoloba gum
Pertinent medical history: T2DM, hypertension, arrhythmia, conduction disturbance, ischemic heart disease, coronary artery bypass graft (2007), incision and drainage of brain abscess twice (1949), hypercholesterolemia, other diabetic neuropathy, hearing loss, upper temporal quadratopia of right eye, diarrhea, rheumatoid arthritis, epilepsy, intermittent headache, cognitive disorder, depression, insomnia, erectile dysfunction, non ST elevation myocardial infarction (March 2010)

A 76-year old man experienced vomiting, nausea, and diarrhea on Day 21; his glucose was 147 mg/dL (morning), 425 mg/dL (lunch), and 371 mg/dL (dinner). Diarrhea and vomiting continued on Day 22, blood glucose in the morning was 348 mg/dL and he didn't take his usual dose of insulin aspart or glargine. He was hospitalized due to diabetic ketoacidosis (DKA) and dehydration on Day 22, and his CKMB levels were elevated (12.4 mcg/L at 4:15, 17 mcg/L at 7:43, and 17.9 mcg/L [normal <7 mcg/L] and CK levels were 132, 181 and 215 IU/L [normal <250 IU/L]). The ECG showed ST depression in V4-V6 which resolved on repeat ECG, but troponin T levels increased (>0/17, 0.25, and 0.43 mcg/L [normal <0.02 mcg/L). Echocardiography showed mild dilated left and right atrium, mitral regurgitation and tricuspid regurgitation, and he was diagnosed with non-ST elevation MI. DKA and dehydration resolved on Day 27 and the study drug was restarted on Day 28. Study drug was permanently discontinued on Day 48 due to DKA.

Reviewer's comment: Vomiting, nausea, and diarrhea may have led to dehydration, DKA, and MI in this patient. Gastrointestinal adverse events including nausea, diarrhea, and vomiting have been reported with canagliflozin, and its role in the reported event cannot be ruled out.

Subject (b) (4); Treatment Canagliflozin 100 mg

Background AHA therapy: glipizide (10 mg), metformin hydrochloride (2000 mg)
Concomitant medications: From baseline: alprazolam, atenolol, lisinopril, atorvastatin calcium, testosterone
Pertinent medical history: T2DM, hypertension, hypercholesterolemia, myocardial infarction, hypogonadism, anxiety, gynecomastia, balinitis, circumcised

A 61-year old man was taken to the emergency room on Day 24 with complaints of retrosternal chest discomfort and pressure that radiated to the shoulders. He had accompanying severe diaphoresis, nausea, vomiting, and shortness of breath. His BP was 150/70, pulse 80, (baseline BP was 98/70, pulse 89) and oxygen saturation was 98% with face mask. ECG showed normal sinus rhythm with marked 8 mm ST elevations in the anterior leads with reciprocal changes inferiorly. At admission, the CK was elevated (10,296 U/L; normal 55-170 U/L), CK-MB was >600 ng/mL (normal <5 ng/mL) and troponin I was >41 ng/mL (normal ≤0.05 ng/mL). By Day 26, CK and CK-MB decreased to 1049 U/L and 12 ng/mL respectively, whereas troponin I level remained elevated. On Day 24, he underwent PCI of LAD and circumflex artery. LAD was

100% occluded and stent was inserted. Due to persistent arrhythmia, second drug-eluding stent was placed in circumflex artery. Echocardiogram showed anteroapical infarct of moderate degree and left ventricular systolic function with ejection fraction of 45%. He recovered post procedure, was discharged on Day 26, and continued in the study.

Nonfatal Stroke

Subject (b) (4) ; Treatment Canagliflozin 300 mg

Background AHA therapy: insulin human P 26 IU/day
Concomitant medications: From baseline: losartan, carvedilol, indapamide, aspirin, simvastatin, finasteride
Pertinent medical history: T2DM, ischemic heart disease (2004), MI (2004), stroke (2004), hypertension, heart failure NYHA class 2 (2004), tremor, left medial malleous fracture, adenoma of prostate

A 79-year old man, who "felt bad", called ambulance on Day 2 at 3AM. He had dizziness, ataxia, and disorientation, with BP of 190/100 mmHg (baseline BP was 160/70). Medications (unknown) was administered by the ambulance service, he felt better, was admitted at 3PM. MRI was not done. He was discharged on Day 16. The final diagnosis was <u>ischemic cerebral stroke</u> of anterior cerebral artery, with discirculatory encephalopathy of hypertonic and atherosclerotic origin. Study drug was never interrupted and he continues in the study. Subsequently, he experienced hypoglycemia (Day 38), creatinine and urea increase (Day 43), and hypotension (Day 112), chronic urinary difficulty and left hydronephrosis (Day 696).

Subject (b) (4) Treatment canagliflozin 100 mg

Background AHA therapy: Levemir (14 IU/day), metformin extended release (2000 mg)
Concomitant medications: From baseline: atorvastatin calcium, irbesartan, hydrochlorothiazide, acetylsalicylic acid, clopidogrel, amlodipine
Pertinent medical history: T2DM (1985), MI (2009), cardiac stent (2009), hypertension (2002), hyperlipidemia (2002), depression (2001), vaginal thrush (1995)

A 68-year old woman presented with a 24-hour history of sudden-onset left arm ataxia and unsteady gait on Day 2, without dizziness, headache, dysphagia, limb weakness, diplopia, or paresthesia. A brain CT showed no recent intracranial event. MRI on Day 3 showed a small area of acute evolving infarction involving the central aspect of right thalamus and extending down into the lateral aspect of right cerebral crus. She continued aspirin, clopidogrel, and study drug. She was discharged on Day 5 and continuing the study.

Subject (b) (4) Treatment Canagliflozin 100 mg

Background AHA therapy: Baseline: huminsulin 50/50 40, huminsulin R 26, anti-hyperglycemic agents 2000, continuous insulin 2007.
Concomitant medications: From baseline: clopidogrel, acetylsalicylic acid, atorvastatin, metoprolol, ramipril, mecobalamin, pregabalin, thioctic acid, itopride, pantoprazole
Pertinent medical history: constipation, backache, hypertension 2003, MI 2009, diabetes 2000, diabetic neuropathy 2007.

A 68-year old man complained of slurred speech, giddiness, and difficulty walking on Day 7 and was hospitalized. His BP was 90/60 mmHg (baseline 118/83 mmHg). A CT scan on Day 9 showed small ill-defined non-hemorrhagic fresh infarcts in right ganglia and bilateral parietal periventricular regions, along with bilateral white matter hypodense ischemic changes with mild diffuse age-related cerebral atrophy. He was discharged on Day 9 in stable condition and is continuing the study. Subsequently, he also experienced headache (Day 75), obstructive airway disorder (Day 214), ischemic cardiomyopathy (Day 214), pollakiuria (Day 456), and foot fracture (Day 812), and none of them serious. The subject also experienced a second ischemic stroke event on Day 237.

Subject (b) (4) : Treatment Canagliflozin 100 mg

Background AHA therapy: gliclazide 60 mg, metformin immediate release 850 mg
Concomitant medications: From baseline: bisoprolol, enalapril, indapamide, amlodipine
Pertinent medical history: T2DM, stroke (2007), goiter, gypermetropia, blepharitis, sclerosis of retinal vessels, discirculatory encephalopathy (2009)

A 57-year old man experienced left-sided hemiparesis and was diagnosed with hemorrhagic stroke in right middle cerebral artery on Day 26. CT on Day 26 showed signs of acute deficiency of cerebral circulation in the projection of the subcortical structures with a breakthrough in the ventricular system; parenchymatous-ventricular hemorrhage; gliomesodermal changes in the projection of the pons on the right; encephalopathy. Doppler ultrasound of neck and brain on Day 28 showed no occlusion or stenotic lesions or arterial/venous malformations. Baseline blood pressure was 177/93; blood pressure at the time of event was unavailable. He was treated with medical therapy, massage, and therapeutic exercises, improved, and discharged on Day 43. He is continuing in the study.

Subject (b) (4) ; Treatment Canagliflozin 300 mg

Background AHA therapy: metformin (1700 mg), gliclazide (60 mg), insulin glargine (18 IU/day)
Concomitant medications: From baseline: metoprolol, rosuvastatin, enalapril, levothyroxine, clopidogrel, acetylsalicylic acid , fosinopril, felodipine, metoprolol
Pertinent medical history: hypothyroidism, cholelithiasis, chronic cerebral ischemia, arrhythmia or conduction disturbance 2002, chronic atrial fibrillation s/p radio ablation and pacemaker, hyperlipidemia 2009, hypertension 1999, MI 2002, diabetes 1999, diabetic nephropathy 2010, diabetic retinopathy 2010, and other diabetic neuropathy 2010

A 56-year old man had stroke on Day 29 without hospitalization or doctor's visit. During a regular study visit a neurologist examined him and confirmed that he had stroke on Day 29. He was hospitalized on Day 45, and he was determined to had an acute cerebrovascular accident in the system of the MCA on the right, of a mixed type, left-sided hemiparesis, mostly in the arm. Brain CT on Day 55 showed signs of chronic cerebrovascular disease with the presence of small areas of decreased density in the plane of basal nuclei on both sides, pinpoint indurations in the basal nuclei on the right. He was discharged on Day 58 and is continuing in the study. Subsequently, he had adverse events of urethritis (Day 324), dizziness during walking (Day 609), heart failure (Day 627), none of which were serious.

Hospitalized Unstable Angina

Subject (b) (4) ; Treatment Canagliflozin 100 mg

Background AHA therapy: glibenclamide (15 mg/day), metformin (2000 mg), aspart insulin (44-70 IU/day)

A 65-year old man with no other significant past medical history other than diabetes developed severe chest pain and was hospitalized on Day 2. EKG showed no indication of MI or ischemia and the cardiac enzymes were normal (value not provided). Coronary angiography done same day showed 90% obstruction of left coronary artery, 99% obstruction of descending artery. He was hospitalized and treated with vasodilators. His baseline BP was 139/81 mmHg; BP at the time of event was unavailable. Doppler ultrasound of neck on Day 9 showed diffuse myointimal thickening of common and internal right and left carotid arteries. Echocardiogram on Day 10 showed slight impairment in systolic pulmonary pressure and diastolic dysfunction with prolonged relaxation rate. He underwent triple coronary artery bypass on Day 17. Study drug was interrupted on Days 17-20, he is continuing in the study after discharge (Day 21).

Subject (b) (4) ; Treatment Canagliflozin 100 mg

Background AHA therapy: insulin glargine 40 U, metformin 2000 mg, glimepiride 6 mg
Concomitant medications: From baseline: levothyroxine, losartan, HCTZ, amlodipine, bisoprolol
Pertinent medical history: T2DM (1998), hypertension (1998), non-specific chest pain (2007) and hypothyroidism (2010); past history of smoking

A 57-year old man experienced chest pain on Day 14 and was hospitalized. Coronary angiography showed stenosis in several coronary arteries. His medication was adjusted (not specified) and was discharged the same day; he underwent PCTA on Day 37. Direct stenting of ramus diagonalis and right coronary artery, and stenting after ballooning of ramis circumflexus and margo obtusus were done, which was complicated by dissection and no reflow of ramus circumflexus. However, there were no clinical complications and he was discharged next day with clopidogrel, aspiring, and statin. He discontinued the study on Day 85 (reason not provided).

One subject in the placebo group who experienced nonfatal myocardial infarction

Subject (b) (4) ; Treatment Placebo

Background AHA therapy: metformin (2000 mg), glipizide (40 mg), pioglitazone (30 mg)
Concomitant medications: From baseline: clopidogrel, isosorbide mononitrate, losartan potassium, metoprolol tartrate, naproxen, nitroglycerin, omeprazole, simvastatin, aspirin, triamcinolone acetonide
Pertinent medical history: T2DM (1996), osteoarthritis (1996), cataracts (2000), hypertension (2009), coronary artery disease (2009), hyperlipidemia (2009), acid reflux (2009) and colon polyps (2010), and previous shingles (2004)

A 67-year old man presented to emergency department on Day 23 with after having episodic chest pain, diaphoresis, and dyspnea lasting 30 minutes during previous night. ECG showed bundle branch block. Echocardiogram showed left ventricular ejection fraction of 40-45%. Cardiac enzymes were "elevated at 0.63" (normal range not provided). Cardiac angiography

showed severe two-vessel coronary artery disease. Stents were placed in LAD artery and distal right coronary artery. He recovered and was discharged on Day 25.

3.14 Significant Laboratory Changes of Interest

Mean change over time in serum electrolytes

The mean change in laboratory values over time is based on data from Placebo-controlled Studies (DS1), since trials in DS2 and DS3 had different time and event schedule for laboratory assessments. Changes related to liver function tests were already discussed in section 3.9 (Hepatic Safety), changes related to calcium and phosphate were already discussed by Dr. Stephen Voss, and changes related to renal function were already discussed by Dr. Aliza Thompson. Here, we mainly discuss changes in electrolytes since canagliflozin acts as an osmotic diuretic.

The mean change in serum electrolytes are summarized in Table 47. As noted, magnesium levels with canagliflozin had the most elevations (7.3 and 8.8% with 100 mg and 300 mg) at the end of 26 weeks of study period, compared to placebo (-1%). The change in magnesium occur by Week 6 with canagliflozin, and remained elevated at similar magnitude throughout 26 weeks of study period.

Although the relative increase in potassium levels with canagliflozin at the end of Week 26 were not largely different from placebo, it should be noted that the maximal elevation in potassium occurs at the first assessment timepoint at Week 6, and then improves over time. At Week 6, the change from baseline was 0.11 and 0.14 mEq/L with canagliflozin 100 mg and 300 mg respectively compared to 0.09 mEq/L in placebo. This translates to 2.6% and 3.3% from baseline for canagliflozin 100 mg and 300 mg respectively, compared to 2% from baseline for placebo at Week 6.

Minimal changes occurred with canagliflozin on serum sodium levels (data not shown).

Table 48: Changes in Serum Electrolytes: Mean and Mean Percent Change from Baseline at Week 26, Regardless of Rescue, DS1

	Placebo	Cana 100 mg	Cana 300 mg
Serum Calcium (mg/dL)	526	715	720
Mean baseline	9.72	9.68	9.68
Mean change from baseline at Week 26	0.01	0.06	0.10
Mean % change	*0.1%*	*0.6%*	*1.0%*
Serum Chloride (mEq/L)	526	715	720
Mean baseline	101.8	101.7	101.9
Mean change from baseline at Week 26	-0.1	0.4	0.4
Mean % change	*-0.1%*	*0.4%*	*0.4%*
Serum Bicarbonate (mEq/L)	523	710	716
Mean baseline	22.40	22.61	22.44
Mean change from baseline at Week 26	0.55	0.15	0.03
Mean % change	*2.5%*	*0.7%*	*0.1%*
Serum Magnesium (mg/dL)	526	714	720
Mean baseline	1.93	1.91	1.93
Mean change from baseline at Week 26	-0.02	0.14	0.17
Mean % change	*-1.0%*	*7.3%*	*8.8%*
Serum Potassium (mEq/L)	523	712	716
Mean baseline	4.3	4.3	4.3
Mean change from baseline at Week 26	0.01	0.01	0.02
Mean % change	*0.2%*	*0.2%*	*0.5%*
Serum Phosphate (mg/dL)	526	715	718
Mean baseline	3.64	3.64	3.62
Mean change from baseline at Week 26	0.02	0.09	0.15
Mean % change	*0.5%*	*2.5%*	*4.1%*
Serum Sodium (mEq/L)	526	715	720
Mean baseline	139.5	139.7	139.7
Mean change from baseline at Week 26	0	0.2	0.2
Mean % change	*0*	*0.1%*	*0.1%*

Source: ISS, DLAB01C_01

The changes in magnesium and potassium were noted to be of possible clinical significance. Changes in potassium and magnesium in DIA3004 are further reviewed since these electrolyte imbalances may be more pronounced in subjects with moderate renal impairment, and in DIA3008 since it would provide change over longer duration in subjects with more comorbidities. In addition, adverse events that may be related to elevated potassium or magnesium levels are discussed.

Hypermagnesemia

The mean changes in magnesium in DIA3004 and DIA3008 are summarized in Table 49. Compared to DS1, there was a slight higher mean change in magnesium with canagliflozin among subjects enrolled in DIA3004 and DIA3008 at the end of Week 26, as summarized in Table 49.

Table 49: Changes in Magnesium (mg/dL) in DIA3004 and DIA3008

	Placebo	Cana 100 mg	Cana 300 mg
DIA3004	78	73	80
Mean baseline	1.98	2.05	2.00
Mean change from baseline at Week 26	0	0.17	0.28
Mean % change	*0*	*8.3%*	*14%*
DIA3008	456	490	477
Mean baseline	1.90	1.92	1.91
Mean change from baseline at Week 26	0	0.16	0.21
Mean % change	*0*	*8.3%*	*11%*

Source: DIA3008 CSR, DLAB51R_CNV; DIA3004 CSR, DLAB01RM_CORE_CNV

No subjects met the PDLC criteria for serum magnesium elevations with canagliflozin in DS1, but more subjects met the PDLC criteria for serum magnesium elevations in DS2 and DS3, as shown in Table 50. In DS3, the incidence of subjects with PDLC of magnesium with canagliflozin 100 mg were comparable to placebo, and the highest incidence was observed with canagliflozin 300 mg. However, the incidence of consistent elevations (reflected in the last post-baseline value) appear to be low overall.

There was no adverse events related to elevated magnesium levels (adverse event terms of hypermagnesemia or blood magnesium increased) in DS1, DS2, or DS3, and only one subject experience hypermagnesemia in DS4 with canagliflozin 100 mg.

Table 50: Subjects (N [%]) with Serum Magnesium Outside Pre-Defined Limits - Regardless of Rescue

	Placebo/ Non-cana	Cana 100 mg	Cana 300 mg
DS2, N	367	332	352
Subjects with 'any' post-baseline >ULN and >25% from baseline	0	5 (1.5)	9 (2.6)
Subjects with 'last' post-baseline >ULN and >25% from baseline	0	2 (0.6)	5 (1.4)
DS3, N	3159	3016	2969
Subjects with 'any' post-baseline >ULN and >25% from baseline	174 (5.5)	165 (5.5)	211 (7.1)
Subjects with 'last' post-baseline >ULN and >25% from baseline	36 (1.1)	35 (1.2)	42 (1.4)

Source: ISS, DLAB02BCNV_02, DLAB02BCNV_03

Hyperkalemia

The mean changes in potassium in DIA3004 and DIA3008 are summarized in Table 51. The changes in potassium levels in DIA3004 over 26 weeks were inconsistent between two canagliflozin groups. Compared to DS1, there was a slight higher mean change in potassium with canagliflozin at the end of Week 26 among subjects enrolled in DIA3008.

Table 51: Changes in Potassium (mEq/L) in DIA3004 and DIA3008

	Placebo	Cana 100 mg	Cana 300 mg
DIA3004	77	72	79
Mean baseline	4.69	4.63	4.56
Mean change from baseline at Week 26	0.02	-0.03	0
Mean % change	*0.4%*	*-0.6%*	*0*
DIA3008	456	488	474
Mean baseline	4.42	4.36	4.39
Mean change from baseline at Week 26	0	0.02	0.03
Mean % change	*0*	*0.5%*	*0.7%*

Source: DIA3008 CSR, DLAB51R_CNV; DIA3004 CSR, DLAB01RM_CORE_CNV

As previously noted, the maximal increase for potassium occurs early post dose, so PDLC analysis would be more relevant to evaluate any clinically significant changes that may occur with potassium levels during canagliflozin therapy. Summary of subjects who met PDLC criteria for serum potassium in DS1, DS2, and DS3 is presented in Table 52. Although there a higher incidence of subjects with serum potassium elevations meeting PDLC criteria with canagliflozin 300 mg compared to the other groups, the incidence was comparable between canagliflozin 100 mg and placebo.

Table 52: Subjects (N [%]) with Serum Potassium Outside Pre-Defined Limits - Regardless of Rescue

	Placebo/ Non-cana	Cana 100 mg	Cana 300 mg
DS1, N	624	809	805
Subjects with 'any' post-baseline >ULN and >15% from baseline	30 (4.8)	36 (4.4)	56 (7.0)
Subjects with 'last' post-baseline >ULN and >15% from baseline	2 (0.3)	7 (0.9)	10 (1.2)
DS2, N	366	332	351
Subjects with 'any' post-baseline >ULN and >15% from baseline	29 (7.9)	24 (7.2)	42 (12.0)
Subjects with 'last' post-baseline >ULN and >15% from baseline	11 (3.0)	6 (1.8)	11 (3.1)
DS3, N	3159	3016	2969
Subjects with 'any' post-baseline >ULN and >15% from baseline	174 (5.5)	165 (5.5)	211 (7.1)
Subjects with 'last' post-baseline >ULN and >15% from baseline	36 (1.1)	35 (1.2)	42 (1.4)

Source: ISS, DLAB02B_01, DLAB02BCNV_02, DLAB02BCNV_03

Adverse events related to elevated potassium levels (event terms of hyperkalemia and blood potassium increased) in DS1, DS2, DS3, and DS4 are presented in Table 53. The incidence of adverse events related to high potassium levels were overall low, with a higher incidence in subjects with moderate renal impairment (e.g., DS2). Similar to PDLC changes, a slightly higher incidence of adverse events related to hyperkalemia was observed with canagliflozin 300 mg compared to canagliflozin 100 mg or placebo.

In DS1, no hyperkalemia was serious, and two events in canagliflozin 300 mg led to treatment discontinuation. In DS2, three hyperkalemia events (one in 100 mg and two in 300 mg) were serious and two hyperkalemia events led to discontinuation, both with canagliflozin 300 mg. None of blood potassium increased were serious or led to discontinuation.

In DS3, a higher incidence of hyperkalemia occurred in canagliflozin 300 mg group compared to non-canagliflozin group, although the difference between treatment groups was not large. Three

hyperkalemia events were serious (one in 100 mg and two in 300 mg). All three had baseline moderate renal impairment. Two of these subjects were also on diuretics and renin-angiotensin agents, and experienced severe hyperkalemia (>7 mEq/L). Third subject also had mild renal function (eGFR 55 mL/min/17.3m2) and was on ACE inhibitor, and developed worsening renal insufficiency with potassium of 5.8 mEq/L. Two events of hyperkalemia also led to discontinuation, both with canagliflozin 300 mg. A significantly higher incidence of blood potassium increased also occurred in DS3; three events led to discontinuation (two with canagliflozin 300 mg and one with non-canagliflozin).

The incidence of hyperkalemia were slightly higher in DS4 compared to DS3, and showed similar trend with DS3. The imbalance in the incidence of blood potassium increased remained not favoring canagliflozin. There were no additional subjects who discontinued in DS4.

Table 53: Hyperkalemia-related Adverse Events - Regardless of Rescue

	Placebo/ Non-cana	Cana 100 mg	Cana 300 mg	All-cana
DS1	N=646	N=833	N=834	N=1667
Hyperkalemia, n (%)	0	5 (0.6)	2 (0.2)	7 (0.4)
Blood potassium increased, n (%)	1 (0.2)	1 (0.1)	4 (0.5)	5 (0.3)
DS2	N=382	N=338	N=365	N=703
Hyperkalemia, n (%)	6 (1.6)	5 (1.5)	8 (2.2)	13 (1.8)
Blood potassium increased, n (%)	0	3 (0.9)	4 (1.1)	7 (1.0)
DS3, N	3262	3092	3085	6177
Hyperkalemia, n (%)	15 (0.5)	17 (0.5)	22 (0.7)	39 (0.6)
Blood potassium increased, n (%)	1 (<0.1)	11 (0.4)	10 (0.3)	21 (0.3)
DS4, N	3262	3092	3085	6177
Hyperkalemia, n (%)	21 (0.6)	20 (0.6)	25 (0.8)	45 (0.7)
Blood potassium increased, n (%)	2 (0.1)	12 (0.4)	13 (0.4)	25 (0.4)

Source: ISS, DAE01R_01, DAE01RB_02, DAE01RC_03, DAE01R_04

Overall, the incidence of adverse events related to elevated potassium levels occurred more often in subjects with baseline renal impairment and/or subjects who are receiving concomitant medications that may also precipitate \hyperkalemia. The incidence of increased potassium levels appear to occur more often with canagliflozin 300 mg compared to 100 mg dose.

4 Summary and Conclusion

Canagliflozin is the first-in-class agent of sodium glucose co-transporter 2 inhibitor, proposed for treatment of adults with type 2 diabetes (T2DM) as an adjunct to diet and exercise. The proposed dose is 100 mg and 300 mg to be taken once daily; 100 mg dose is proposed as the starting dose for subjects at risk for volume depletion (e.g., on loop diuretic, moderate renal impairment [e.g., eGFR 30 to <60 mL/min/1.73m^2], and ≥75 years of age). Unlike most other approved non-insulin anti-diabetic drugs, the glycemic efficacy of canagliflozin does not depend on insulin secretion or insulin sensitivity, but does depend on renal function since its efficacy is dependent on the amount of glucose delivered to nephron.

In the clinical development program for canagliflozin, its efficacy was evaluated both as monotherapy and in combination with approved anti-diabetic agents, where canagliflozin was

given as an add-on to metformin, metformin+sulfonylurea, metformin+pioglitazone, and insulin. In addition, the efficacy and safety of canagliflozin in T2DM with moderate renal function (DIA3004) and older adults (DIA3010) were also evaluated. The glycemic efficacy of canagliflozin compared to placebo, as measured by the change in HbA1c from baseline, was observed in all placebo-controlled Phase 3 trials. The placebo-adjusted mean reduction in HbA1c was dose-dependent, and ranged from 0.3 to 0.9% with canagliflozin 100 mg and 0.4 to 1.2% with canagliflozin 300 mg. In two active-controlled trials, the applicant showed that canagliflozin was non-inferior when compared to glimepiride (both doses) and sitagliptin (only 300 mg dose).

Although the glycemic efficacy of canagliflozin in DIA3004 (moderate renal impairment study; baseline eGFR ≥30 to <50 mL/min/1.73m^2) reached statistical significance, the placebo-subtracted change in HbA1c from baseline was modest in this trial compared to other placebo-controlled trials with canagliflozin. The applicant further evaluated glycemic efficacy in this population by constructing a pooled dataset of subjects with moderate renal function (eGFR ≥30 to <60 mL/min/1.73m^2). The placebo-subtracted HbA1c reduction in this pooled dataset was 0.4 and 0.5% with canagliflozin 100 mg and 300 mg, and a subgroup analysis of change in HbA1c by baseline eGFR showed that the glycemic efficacy was further attenuated in the subgroup of subjects at the lower half of moderate renal function (e.g., <45 mL/min/1.73m^2). In this subgroup, the placebo-subtracted LS mean reduction in HbA1c was 0.2% with the lower dose of canagliflozin (100 mg).

Because canagliflozin increases urinary glucose excretion, it can potentially increase fungal growth in perineum and increase bacterial growth in urinary tract. Not surprisingly, treatment with canagliflozin was associated with an increased incidence of urinary tract infection and genital mycotic infections (more in women compared to men) compared to placebo in Phase 3 trials. This increased incidence was not dose-dependent. The incidence of urinary tract infection leading to serious outcome and discontinuation was slightly higher with canagliflozin compared to placebo. All genital mycotic infections that were serious or led to discontinuation only occurred with canagliflozin.

Based on nonclinical data and clinical data from another SGLT2 inhibitor (dapagliflozin), renal, adrenal, testicular, breast, and bladder malignancies were carefully evaluated throughout development of canagliflozin. At the time of this review, available data do not suggest an increased risk of these malignancies with canagliflozin. Although it should be kept in mind that most clinical development program is never big or long enough to detect malignancy potential for a drug product at the time of NDA submission, it is reassuring to observe no imbalance in malignancies with canagliflozin treatment in about 8000 person-years exposure (as of July 1, 2012 at 4-month safety update).

In the clinical program for another SGLT2 inhibitor (dapagliflozin), significant elevations in liver aminotransferases were not observed with the product when compared to placebo; however, a case that met Hy's Law criteria was identified and raised concern with regard to its hepatotoxicity. As reviewed herein, there was an imbalance in marked shifts in transaminases not favoring canagliflozin, but review of cases that met the Biochemical criteria of Hy's law (AST or ALT ≥3x ULN and total bilirubin ≥2x ULN), in consultation with hepatic expert in the

Office of Surveillance and Epidemiology, did not identify any true Hy's law cases. Thus, despite an imbalance of significant elevations in ALT and/or AST not favoring canagliflozin, absence of a Hy's law case is somewhat reassuring.

In nonclinical studies, canagliflozin led to an increase in trabecular bone volume (hyperostosis). In DIA3010, canagliflozin showed placebo-corrected increase in serum CTx (bone resorption marker) which was statistically significant and increase in P1NP (bone formation marker) which did not reach statistical significance. In addition, bone mineral density (BMD) was measure by DXA, and the changes were not consistent or clinically significant at Week 26. However, longer data is required to assess the chronic effect of canagliflozin on BMD. The controlled extension period of DIA3010 will have Week 52 or 104 data. In addition to these bone-related findings, fractures were adjudicated throughout clinical development of canagliflozin, and there was an imbalance in the total fractures and upper extremity fractures not favoring canagliflozin which was not statistically significant. However, as Dr. Voss of DRUP pointed out, the available data may not have enough power to rule out a modest increase in these infrequent events.

Due to its mechanism of action (e.g., increase urinary glucose excretion), canagliflozin acts as an osmotic diuretic with an increase in urinary output. This clearly led to an increased incidence in osmotic diuresis-related and volume depletion-related events in subjects receiving canagliflozin when compared to placebo. The incidence of osmotic diuresis did not appear to be dose-dependent whereas the incidence of volume depletion appeared to be dose-dependent. Subgroup analysis indicated that subjects with low baseline renal function (<60 mL/min/1.73m^2), elderly (≥75 years), and concomitant use of loop diuretics may led to an increased incidence of volume depletion events with canagliflozin, and this risk was dose-dependent. Based on this subgroup analysis, the applicant proposes 100 mg dose of canagliflozin as the starting dose in subjects on loop diuretics, moderate renal impairment, and ≥75 years of age, with titration to 300 mg dose if additional glycemic control is needed. However, it has not been prospectively shown whether this titration of dose would reduce the risk of volume depletion-related adverse events.

Because canagliflozin leads to volume depletion, there is a concern for potential adverse renal effects. In clinical trials, canagliflozin has been associated with dose-dependent decrease in eGFR. However, the pattern of eGFR decline appear to be different in subjects with different baseline renal function. In the Placebo-controlled Studies Dataset (DS1), which included subjects with normal to mild renal function (median eGFR of 86 mL/min/1.73m^2), the nadir in eGFR occurred at the first timepoint of assessment and appear to recover towards baseline over time. However, in DIA3008, which enrolled subjects with moderate renal function (median eGFR of 76 mL/min/1.73m^2), the early drop in eGFR appear to persist over time. In addition, evaluation of marked changes in eGFR showed that the incidence of marked decline in eGFR was similarly greater with both doses of canagliflozin compared to placebo in subjects with moderate renal function (DS2; eGFR 30 to 60 mL/min/1.73m^2).

As pointed out by Dr. Thompson, the long-term renal consequences of canagliflozin are unknown, and the amount of safety data in subjects with moderate renal impairment is limited. Because of increased incidence of volume depletion-related events with canagliflozin in subjects with low baseline eGFR, the applicant proposes 100 mg dose of canagliflozin as the starting dose for subjects with moderate renal function. However, as discussed, the glycemic efficacy in

subjects with moderate renal function is modest, with further attenuation of glycemic efficacy in those at the lower end of moderate renal function (e.g., <45 mL/min/1.73m^2). Thus, subjects with moderate renal function will be at an increased risk for adverse renal events with moderate efficacy. Given the prevalence of renal disease in diabetes and declining renal function with prolonged duration of diabetes, this is problematic since monitoring renal function may be necessary not only to assure safety but also to assure efficacy with chronic use of canagliflozin.

Lastly, canagliflozin increases LDL-C levels. Since LDL-C is a well-established biomarker and changes in this marker appear linearly related to cardiovascular (CV) risk, it is possible that canagliflozin may lead to CV harm despite favorable changes in HDL-C, blood pressure, and body weight. In the CV meta-analysis of Phase 2 and 3 trials, the pre-specified interim analyses of MACE or MACE-plus did not appear to show an increased incidence of composite CV endpoints, and showed non-significant increase in stroke. There is a concern of high MACE events during the first 30 days post-dose with canagliflozin which was observed in DIA3008, and it is unclear whether this is a spurious finding or a true increased risk of early CV events with canagliflozin in patients at high risk for CV event.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Cardiovascular Safety: Statistical Review

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON
Canagliflozin

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory Committee, January 10, 2013

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1. Trial Database

On 31 May 2012, Janssen submitted a meta-analysis of cardiovascular events conducted in nine randomized clinical trials for canagliflozin as part of their application package for NDA 204042. The meta-analysis included one Phase 2 trial (Study DIA2001), seven Phase 3 trials (Studies DIA3002, 3004, 3005, 3006, 3009, 3010 and 3012) and one Phase 3 dedicated cardiovascular safety trial, Study 3008, also referred to as CANVAS. The meta-analysis was conducted in accordance to the FDA Diabetes Guidance for evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (2008). The criteria set forth in the Guidance reads:

> *For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):*
>
> - *Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.*

The data cutoff date for this meta-analysis was 31 January 2012. At that time, only Study DIA2001 had been completed. All other trials in the meta-analysis were still following subjects in a double-blinded manner to assess the safety and tolerability of canagliflozin. CANVAS had finished enrolling subjects, but the trial is currently ongoing and will be completed when a pre-specified number of MACE-plus are observed.

CANVAS was designed to study a population with a higher background CV risk than the other trials in the meta-analysis. The inclusion criteria for CANVAS was: "Men or women with T2DM who have inadequate glycemic control (HbA1c ≥7.0 and ≥10.5%), not on an AHA (antihyperglycemic agent) or on an AHA in monotherapy or combination therapy, and who have known CV disease or who have 2 or more risk factors for CV events."

The meta-analysis was conducted on a modified intent-to-treat (mITT) population consisting of all randomized subjects who took at least 1 dose of the double-blind study medication. A summary of the design characteristics of the nine trials in the meta-analysis is shown in Table 1.

Table 1. List of Trials Included in the CV Meta-Analysis, mITT Population

Trial ID	Phase	Duration of Treatment	Total Sample Size	Canagliflozin (N)		Control (N)		
				100 mg	300 mg	Placebo	Glimepiride	Sitagliptin
DIA2001	2	12 weeks	193	64	64	65	-	-
DIA3002	3	52 weeks	469	157	156	156	-	-
DIA3004	3	52 weeks	269	90	89	90	-	-
DIA3005	3	52 weeks	675	242	241	192	-	-
DIA3006	3	52 weeks	1284	368	367	183	-	366
CANVAS	3	Not fixed	4327	1445	1441	1441	-	-
DIA3009	3	104 weeks	1450	483	485	0	482	-
DIA3010	3	104 weeks	714	241	236	237	-	-
DIA3012	3	52 weeks	342	113	114	115	-	-

Source: Created by reviewer from Integrated Summary of Safety and dataset adttecv.xpt

2. Statistical Methods

2.1 Endpoint

The agreed-upon primary endpoint for CV safety analyses was Major Adverse Cardiovascular Events Plus (MACE-plus), which was defined as a composite endpoint consisting of the following adjudicated events: cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke and hospitalization for unstable angina (HUA).

The primary meta-analysis included all MACE-plus observed while subjects were on study drug or within 30 days of study drug discontinuation.

2.2 Analysis Methods

The pre-specified primary analysis used a stratified Cox proportional hazards model to estimate the hazard ratio (HR) of MACE-plus, and its 95% confidence interval, comparing canagliflozin (combined 100 mg and 300 mg doses) versus all comparators. The model included two strata: CANVAS, non-CANVAS trials.

A secondary stratified Cox proportional hazards model, similar to that for MACE-plus, was fit to estimate the hazard ratio (HR) and 95% confidence interval for MACE.

These analyses were repeated separately in CANVAS alone and in the grouped non-CANVAS trials.

After analyzing the data, the FDA review team found evidence to suggest that the hazard functions for MACE-plus for canagliflozin and comparators are not proportional in CANVAS and in the primary meta-analysis including CANVAS. If the hazard functions are not proportional, the assumptions of the pre-specified Cox proportional hazards model are not met. These issues are discussed in more detail in the next section. To address the violation of proportional hazards in CANVAS, the FDA review team fit the following post-hoc analyses on MACE-plus:

- Cox proportional hazards model during the first 30 days of CANVAS.
- Cox proportional hazards model after the first 30 days in CANVAS for subjects who survived and were being followed in CANVAS at day 30.

3. Results

3.1 Descriptive Statistics of MACE-plus

Table 2 shows the observed number of MACE-plus in the nine trials in the meta-analysis. A total of 130 events were observed among 6396 subjects randomized to canagliflozin and 71 events were observed among 3327 subjects randomized to comparators. The table shows that 161 of the 201 (80%) MACE-plus events were observed among subjects enrolled in CANVAS.

Table 2. Number of Subjects with MACE-plus / Total Subjects

Trial	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Active Comparator
DIA2001	0 /64	0 /64	0 /65	-
DIA3002	1 /157 (0.64%)	0 /156	1 /156 (0.64%)	-
DIA3004	1 /90 (1.11%)	3 /89 (3.37%)	4 /90 (4.44%)	-
DIA3005	0 /242	0 /241	0 /192	-
DIA3006	0 /368	1 /367 (0.27%)	1 /183 (0.55%)	3 /366 (0.82%)
CANVAS	56 /1445 (3.88%)	52 /1441 (3.61%)	53 /1441 (3.68%)	-
DIA3009	5 /483 (1.04%)	4 /485 (0.82%)	-	5 /482 (1.04%)
DIA3010	3 /236 (1.27%)	3 /236 (1.27%)	4 /237 (1.69%)	-
DIA3012	0 /114	1 /114 (0.88%)	0 /115	-
Total:	66 / 3203 (2.06%)	64 / 3193 (2.00%)	63 / 2479 (2.54%)	8 / 848 (0.94%)

Source: Created by reviewer

Subsection 3.2 of this document shows results from the pre-specified meta-analysis including all trials. Subsection 3.3 discusses the results of the secondary pre-specified Cox proportional hazards model fit to the non-CANVAS trials. Subsection 3.4 shows statistical analyses of CANVAS within 30 days and after 30 days of subjects' first randomized treatment dose.

3.2 Pre-Specified Meta-Analysis of MACE-plus

The pre-specified primary Cox proportional hazards model fit to all trials including CANVAS obtained an estimated hazard ratio and 95% confidence interval of **0.91 (0.68, 1.22)** for the risk of MACE-plus comparing canagliflozin to all comparators as shown in Table 3. There is evidence to suggest that the assumption of proportional hazards was not met in these data and therefore the pre-specified Cox proportional hazards model may not be appropriate. Therefore, results using alternate analysis methods for CANVAS are presented in Section 3.4.

Table 3. Number of Events (Rate per 1000 Patient-Years) in All Trials in the Pre-Specified Meta-Analysis

	Canagliflozin N= 6396 PY = 6876	Comparators N = 3327 PY = 3470	Hazard Ratio (95% CI)
MACE-plus	**130 (18.9)**	**71 (20.5)**	**0.91 (0.68, 1.22)**
CV Death	21 (3.1)	16 (4.6)	0.65 (0.34, 1.24)
MI	45 (6.5)	27 (7.8)	0.83 (0.51, 1.34)
Stroke	47 (6.8)	16 (4.6)	1.46 (0.83, 2.58)
Hospitalized unstable angina	26 (3.8)	18 (5.2)	0.71 (0.39, 1.30)

Source: Created by reviewer

3.3 Analysis of MACE-plus excluding CANVAS

Figure 1 shows the estimated survival curves for all trials shown in Table 1 excluding the CANVAS trial, hereafter referred to as non-CANVAS trials. Among subjects in the non-CANVAS trials, the estimated cumulative probability of MACE-plus was lower among subjects on canagliflozin than comparators throughout the duration of follow-up.

Figure 1. Estimated Probability and 95% CI of MACE-plus by Time in All Trials excluding CANVAS

Source: Created by reviewer

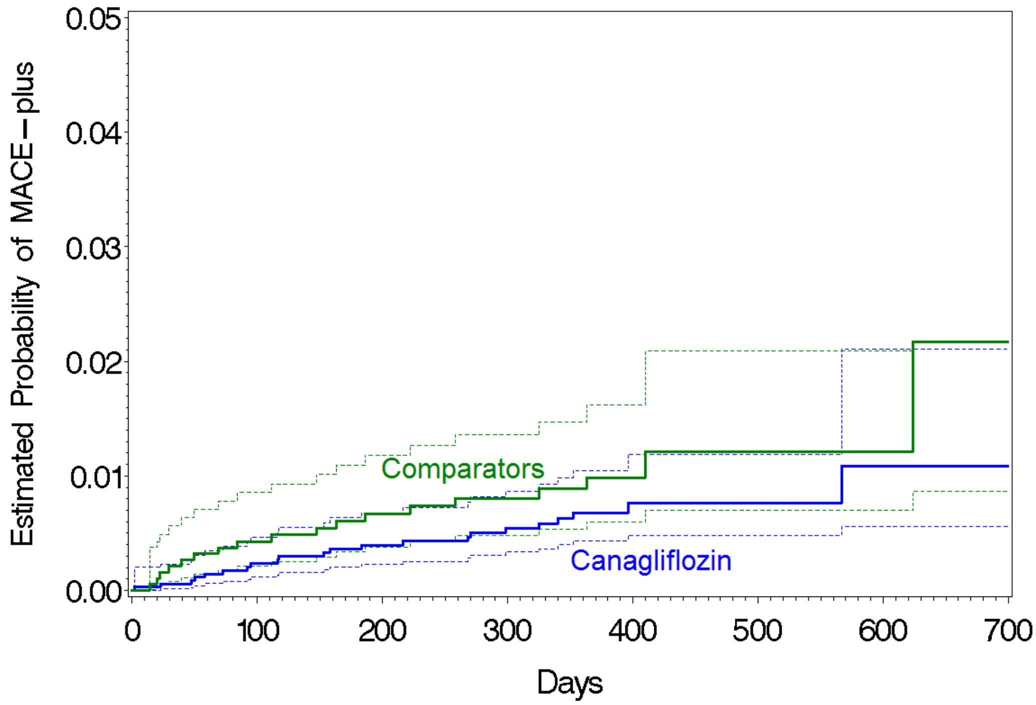


Table 4 shows MACE-Plus observed in non-CANVAS trials. A Cox proportional hazards model was fit to these data to estimate the hazard ratio of MACE-plus associated with canagliflozin relative to all comparators. The estimated hazard ratio and its corresponding 95% confidence interval excluding CANVAS were **0.65 (0.35, 1.21)**. The hazard ratio of the individual components of MACE-plus was not estimated due to the small counts of events. The assumption of proportional hazards appears reasonable in these data (see Figure 1). There is no evidence of early increased risk of MACE-plus associated with canagliflozin in these data.

Table 4. Number of Events (Rate per 1000 Patient-Years) in All Trials Excluding CANVAS

	Canagliflozin N=3510 PY = 3464	Comparators N = 1886 PY = 1806	Hazard Ratio (95% CI)
MACE-plus	**22 (6.4)**	**18 (10.0)**	**0.65 (0.35, 1.21)**
CV Death	2 (0.6)	2 (1.1)	
MI	7 (2.0)	12 (6.6)	
Stroke	9 (2.6)	1 (0.6)	
Hospitalized unstable angina	4 (1.2)	3 (1.7)	

Source: Created by reviewer

3.4 Analysis of MACE-plus in CANVAS

Figure 2 shows the estimated survival curves for MACE-plus in CANVAS. A higher rate of MACE-plus was observed among subjects on canagliflozin during the first 30 days after the first randomized treatment dose, and a lower rate was observed on canagliflozin after 30 days. Figure 2 shows that the assumption of proportional hazards does not hold in CANVAS. Additional diagnostic tests were conducted (not shown here) that suggest that the hazard functions for MACE-plus in CANVAS were not proportional through time when comparing canagliflozin to placebo.

Figure 2. Estimated Probability and 95% CI of MACE-plus by Time in CANVAS

Source: Created by reviewer

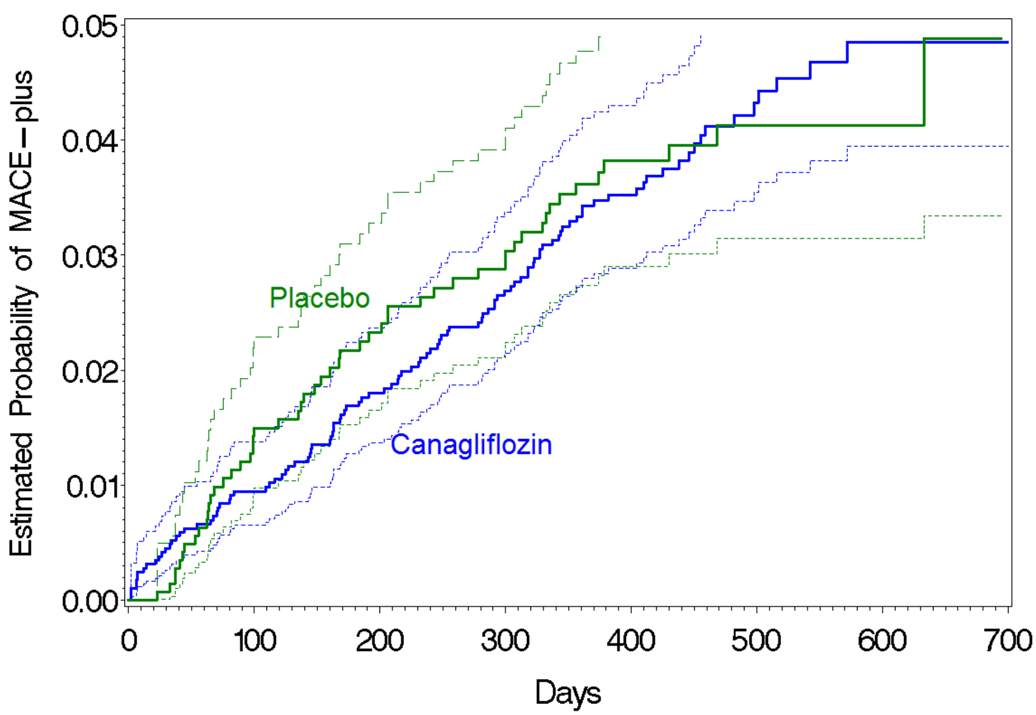


Table 5 shows a list of MACE-plus events observed during the first 30 days after the first randomized treatment dose in CANVAS. The day of first treatment dose is considered "day 1", so that events observed on "day 2" correspond to the day after first treatment dose. During the first 30 days in CANVAS, there were 13 MACE-plus observed among 2886 subjects on canagliflozin (0.45%) and 1 MACE-plus among 1441 subjects on placebo (0.07%). Seven of the 13 MACE-plus on the canagliflozin arm occurred during the first 7 days of study.

After the first 30 days in CANVAS, there were 95 MACE-plus observed in 3176 patient-years of follow-up on canagliflozin (29.9 events per 1000 patient-years) and 52 MACE-plus in 1547 patient-years of follow-up on placebo (33.6 events per 1000 patient-years).

Table 5. List of MACE-plus in CANVAS During the First 30 Days After Randomization

Treatment	Age	Day of Event	Type of Event
Cana 300 mg	79	2	Nonfatal Stroke
Cana 100 mg	65	2	Hospitalized Unstable Angina
Cana 100 mg	68	2	Nonfatal Stroke
Cana 300 mg	57	6	Nonfatal Myocardial Infarction
Cana 300 mg	76	6	Nonfatal Myocardial Infarction
Cana 300 mg	54	7	Cardiovascular Death
Cana 100 mg	68	7	Nonfatal Stroke
Cana 300 mg	37	12	Nonfatal Myocardial Infarction
Cana 100 mg	57	14	Hospitalized Unstable Angina
Cana 100 mg	76	21	Nonfatal Myocardial Infarction
Placebo	67	23	Nonfatal Myocardial Infarction
Cana 100 mg	61	24	Nonfatal Myocardial Infarction
Cana 100 mg	57	26	Nonfatal Stroke
Cana 300 mg	56	29	Nonfatal Stroke

*Sample size = 2886 on canagliflozin and 1441 on placebo.
Source: Created by reviewer

In the following subsections, 3.4.1 and 3.4.2, the risk of MACE-plus in CANVAS is analyzed separately within the first 30 days of the study, and after 30 days in the study. These are post-hoc analyses conducted by the review team at the FDA after reviewing the submitted data.

3.4.1 Analysis of the First 30 Days in CANVAS

An imbalance of MACE-plus was observed during the first 30 days of treatment in CANVAS as shown earlier in Figure 2. A Cox proportional hazards model was fit to these data to estimate the hazard ratio of MACE-plus associated with canagliflozin during the first 30 days of this trial. The estimated hazard ratio and its corresponding 95% confidence interval were **6.50 (0.85, 49.66)**. Note that due to the small number of events in this analysis, the estimated hazard ratio is highly sensitive to any additional events. For

example, one additional event among subjects on placebo at day 15 would result in a hazard ratio of 3.25 (0.73, 14.39), two events would result in a hazard ratio of 2.16 (0.62, 7.59) during the first 30 days. Due to the small number of events within this time window, and as represented by the wide confidence interval of the hazard ratio, these findings cannot definitely conclude a significant increase in risk within 30 days associated with canagliflozin. It is possible that the observed imbalance of MACE-plus in the first 30 days of CANVAS might be attributable to chance.

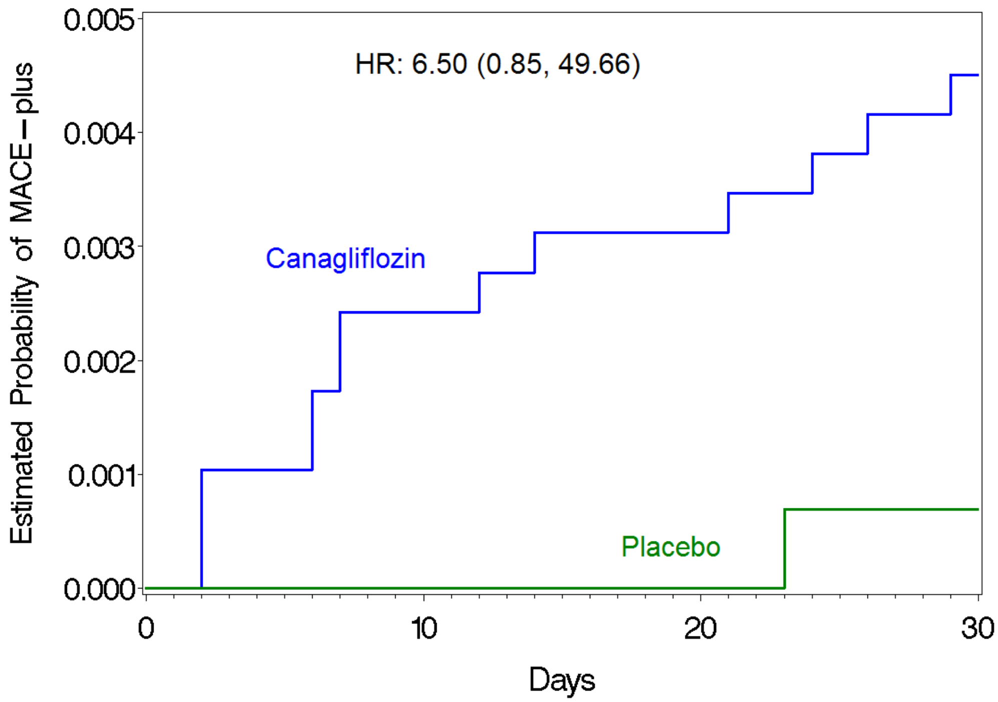
Table 6. First 30 Days in CANVAS

	Canagliflozin	Placebo
N	2886	1441
Events (events per 1000 patients)	13 (4.5)	1 (0.7)
HR (95% CI)	**6.50 (0.85, 49.66)**	

Source: Created by reviewer

Figure 3. Estimated Probability and 95% CI of MACE-plus During the First 30 Days of CANVAS

Source: Created by reviewer



3.4.2 Analysis After Day 30 in CANVAS

Figure 4 shows the estimated survival curve for MACE-plus after 30 days for subjects in CANVAS who did not have an event and did not drop-out of the study during the first 30 days. A Cox proportional hazards model was fit to these data to estimate the hazard ratio of MACE-plus associated with canagliflozin. The estimated hazard ratio and its

corresponding 95% confidence interval were **0.89 (0.64, 1.25)**. These data show no evidence of increased risk associated with canagliflozin.

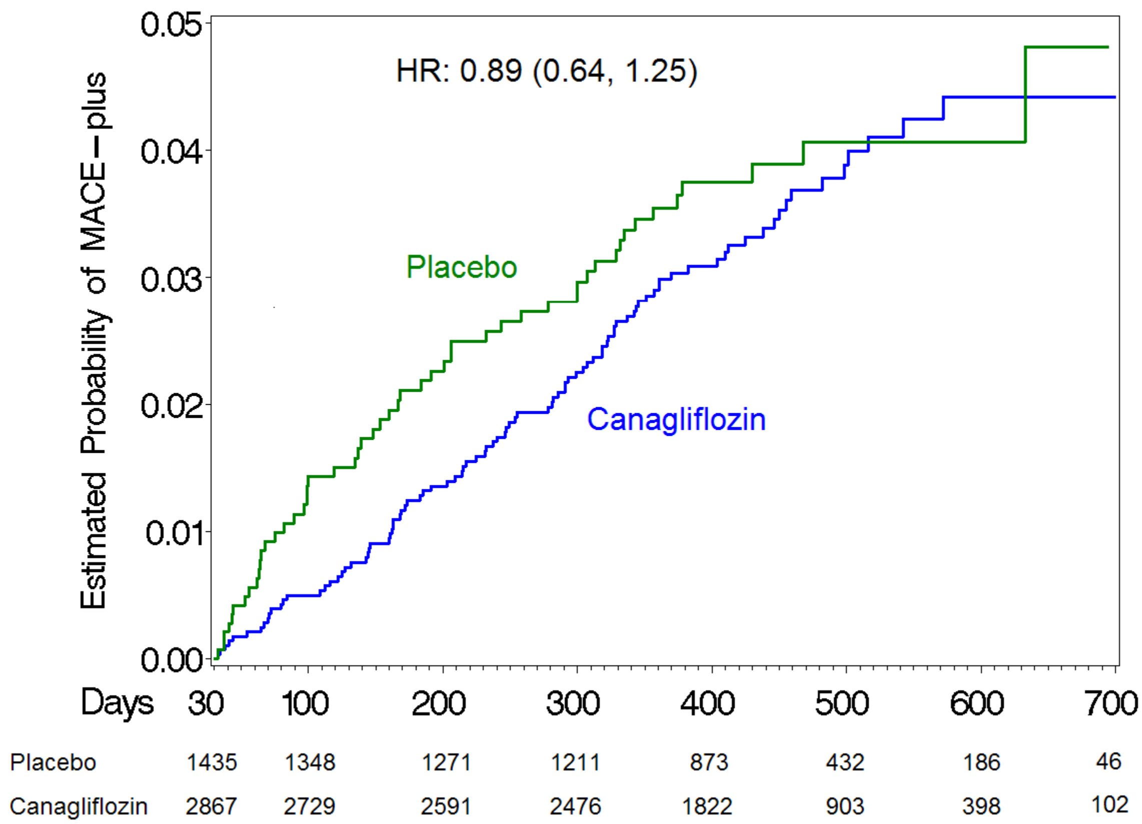
Table 7. Number of Events (Rate per 1000 Patient-Years) after Day 30 in CANVAS

	Canagliflozin N= 2867 PY = 3175	Comparators N = 1435 PY = 1546	Hazard Ratio (95% CI)
MACE-plus	**95 (29.9)**	**52 (33.6)**	**0.89 (0.64, 1.25)**
CV Death	18 (5.7)	14 (9.1)	0.63 (0.31, 1.26)
MI	33 (10.4)	13 (8.4)	1.24 (0.65, 2.35)
Stroke	31 (9.8)	15 (9.7)	1.01 (0.55, 1.87)
Hospitalized unstable angina	20 (6.3)	15 (9.7)	0.65 (0.33, 1.27)

Source: Created by reviewer

Figure 4. Estimated Probability and 95% CI of MACE-plus in CANVAS Among Subjects who Survived and were Followed at Day 30

Source: Created by reviewer



4. Summary of Findings

The pre-specified analysis to assess cardiovascular safety of canagliflozin called for a Cox proportional hazards model including data from 9 trials. There is evidence to suggest that the assumption of proportional hazards necessary to interpret the Cox model in the pre-specified analysis was not met because of an imbalance of MACE-plus within the first 30 days of the dedicated cardiovascular trial, CANVAS.

During the first 30 days of CANVAS, 13 MACE-plus were observed among 2886 subjects on canagliflozin and 1 MACE-plus was observed among 1441 subjects on placebo. This imbalance may be attributable to chance or may have been caused by an early increase in the risk of MACE-plus associated with canagliflozin among subjects with high background cardiovascular risk. There was no evidence of an increased risk of MACE-plus associated with canagliflozin after 30 days in CANVAS.

There was no evidence of an increase in the risk of MACE-plus associated with canagliflozin in the non-CANVAS trials either in the first 30 days or overall. The overall estimated hazard ratio of MACE-plus and its corresponding 95% confidence interval in trials excluding CANVAS were **0.65 (0.35, 1.21)**.

Appendix 1:

Renal Safety Review

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date:	December 2, 2012
From:	Aliza Thompson, MD, Medical Officer Division of Cardiovascular and Renal Products
Through:	Norman Stockbridge, MD, PhD, Director Division of Cardiovascular and Renal Products
To:	Jena Weber, Regulatory Project Manager Division of Metabolic and Endocrine Products
Subject:	Consult to evaluate and comment on the renal safety findings associated with canagliflozin use in NDA 204042

Background
Canagliflozin is an inhibitor of sodium-glucose transporter 2 (SGLT2) and has been developed by the applicant to improve glycemic control in adults with type 2 diabetes mellitus (NDA submitted in May 2012). The SGLT2 transporter in the proximal renal tubule is thought to reabsorb the majority of glucose filtered by the renal glomerulus. SGLT2 inhibitors lower plasma glucose levels by decreasing renal glucose re-absorption. Although there are no approved agents in this class in the U.S., there are other SGLT2 inhibitors in various stages of development.

Because of their mechanism of action, intravascular volume depletion has been a concern with SGLT2 inhibitors. There has also been concern for potential adverse renal effects secondary to volume depletion. In the canagliflozin development program, an early and dose-dependent increase in serum creatinine and BUN levels was observed. Early and dose-dependent increases in creatinine were also reported in the development program of another SGLT2 inhibitor, dapaglifozin (see FDA Briefing Document for NDA 202293, Dapaglifloizin tablets, ACM July 19, 2011).

This consult from the Division of Metabolic and Endocrine Drug Products asks for comment from the Division of Cardiovascular and Renal Products on the renal safety findings in the canagliflozin development program, as well as their clinical significance.

Sources of data

In support of the proposed indication, the applicant conducted nine phase 3 trials in subjects with type 2 diabetes using the doses of canagliflozin proposed in labeling (100 mg and 300 mg). An overview of these trials is provided in the table below. Four of these trials had a placebo control and excluded subjects with an eGFR < ~50-60 mL/min/1.73 m^2. Two were active-controlled and also excluded subjects with an eGFR in the aforementioned range. In addition, three placebo-controlled trials were conducted/are underway in special populations as defined by age, renal impairment and cardiovascular risk. The trial conducted in subjects with moderate renal impairment (DIA3004) enrolled subjects with an eGFR ≥30 and <50 mL/min/1.73 m^2. The applicant's cardiovascular outcome study (DIA3008) allowed enrollment of subjects with an eGFR <30 mL/min/m^2. The trial conducted in older subjects excluded subjects with an eGFR <50 mL/min/m^2.

Table 1. Overview of Phase 3 studies in subjects with type 2 diabetes mellitus

Study / Population	Background Therapy	Design/Duration[a]	Number of Randomized Subjects	Study Treatment Groups
		Phase 3 Placebo–controlled Studies		
DIA3005 (general T2DM) Main Study	Diet/exercise	Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=587 (excluding high glycemic cohort)	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
High Glycemic Cohort	Diet/exercise	26 weeks double-blind	N=91	1) Canagliflozin – 100 mg 2) Canagliflozin – 300 mg
DIA3002 (general T2DM)	Metformin and sulphonylurea	Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=469	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA3006[b] (general T2DM)	Metformin	Placebo- and active-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=1284	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg 4) Sitagliptin – 100 mg
DIA3012 (general T2DM)	Metformin and pioglitazone	Placebo-controlled 52 weeks double blind (26 weeks core/26 weeks extension period)	N=344	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
		Phase 3 Active–controlled Studies		
DIA3009 (general T2DM)	Metformin	Active-controlled 104 weeks double blind (52 weeks core/52 weeks extension period)	N=1452	1) Canagliflozin – 100 mg 2) Canagliflozin – 300 mg 3) Glimepiride (titrated 1 mg up to a maximum[c] of 6 to 8mg)
DIA3015 (general T2DM)	Metformin and sulphonylurea	Active-controlled 52 weeks double blind	N=756	1) Canagliflozin – 300 mg 2) Sitagliptin – 100 mg

Table 1 Continued

Study / Population	Background Therapy	Design/Duration[a]	Number of Randomized Subjects	Study Treatment Groups
		Phase 3 Studies in Special Populations		
DIA3010 (T2DM / older [≥55 years] subjects)	Any diabetes therapy (diet or oral or parenteral AHA)	**Older Subjects (ie, ≥55 to ≤80 years of age) /Bone Density Evaluation** Placebo-controlled 104 weeks double blind (26 weeks core/78 weeks extension period)	N=716	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA 3004 (T2DM with moderate renal impairment population)	Any diabetes therapy (diet or oral or parenteral AHA)	**Study in Subjects with Moderate Renal Impairment** Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=272	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA3008[d] (T2DM with CV disease or at high risk for CV disease)	Any diabetes therapy (diet or oral or parenteral AHA) Substudies: On insulin (≥20 units/day On SU agent (defined doses)	**Cardiovascular Study – Including 2 Efficacy and Safety Sub-studies (Insulin; SU)** Placebo-controlled, double-blind Event-driven; estimated duration of 4 to 8 years Duration of efficacy substudies: 18 weeks	N=4330 (total)	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg

AHA= antihyperglycemic agent

a All studies were multicenter, parallel-group studies; all canagliflozin doses are once-daily

b Study DIA3006 was both placebo- and active controlled.

c The maximum dose allowed based on the approved country-specific label

d The six strata in DIA-3008 were defined as:

Stratum 1: insulin monotherapy ≥20 units per day, on stable doses at least 10 weeks before the run-in visit

Stratum 2: insulin ≥20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy

Stratum 3: insulin ≥20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit

Stratum 4: sulphonylurea monotherapy, on stable doses at least 10 weeks before the run-in visit

Stratum 5: PPARγ agonist (pioglitazone ≥30 mg/day or rosiglitazone ≥4 mg/day) plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other background AHA therapy, on stable doses at least 10 weeks before the run-in visit

Stratum 6: subjects not in one of the above AHA subgroups

Source: Summary of Clinical Safety, Table 2

The pooled datasets described below are referenced in this review. Results of some individual studies are also discussed.

- Placebo-controlled studies dataset (DS1)- includes data to week 26 from the four placebo-controlled phase 3 studies that excluded subjects with an eGFRs <~50-60 mL/min/1.73^2 (DIA3002, DAI3005, DIA3006 and DIA3012). The median age in this dataset is 57 and median baseline eGFR is 86 mL/min/1.73^2.
- Moderate renal impairment dataset (DS2)- includes data from subjects with a baseline eGFR ≥30 to < 60 mL/min/1.73m^2 (DIA3004 and a subset of subjects enrolled in DIA3005, DIA3008 and DIA3010; data up to the data cut-off date of September 15, 2011 for DIA3008 and up to week 26 for the other studies). The median age in this dataset is 67 and median baseline eGFR is 50 mL/min/1.73m^2; approximately one-third of subjects had an eGFR <45 mL/min/1.73m^2. Subjects in this dataset had a mean duration of exposure of 36 and 33 weeks in the canagliflozin and placebo arms, respectively.

Renal safety findings

In phase 1 studies, treatment with canagliflozin was associated with early increases in urine volume and serum creatinine and BUN levels, and decreases in blood pressure. In the phase 3 trials, an early and dose-dependent decrease in eGFR was also observed, which did not appear to worsen with continued therapy. As shown in the figures below, the magnitude of the initial drop in eGFR (relative to placebo) and its pattern/persistence over time, appeared to vary

somewhat, depending upon the population studied. Corresponding treatment-induced changes in BUN (i.e., an early increase and persistent elevation) were also seen.

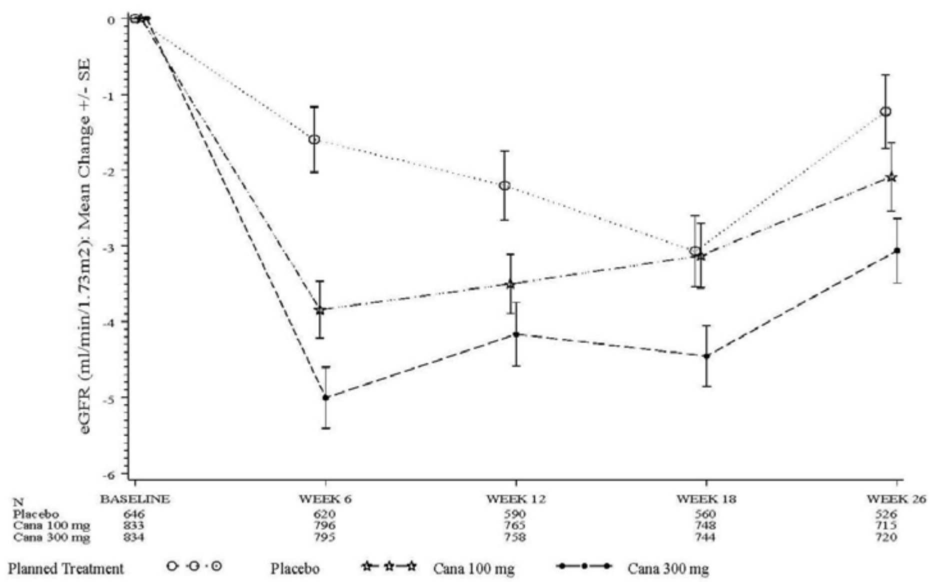


Figure 1. Mean Change (+/-SE) in eGFR from baseline in the placebo-controlled studies dataset
Source: ISS, Figure 18

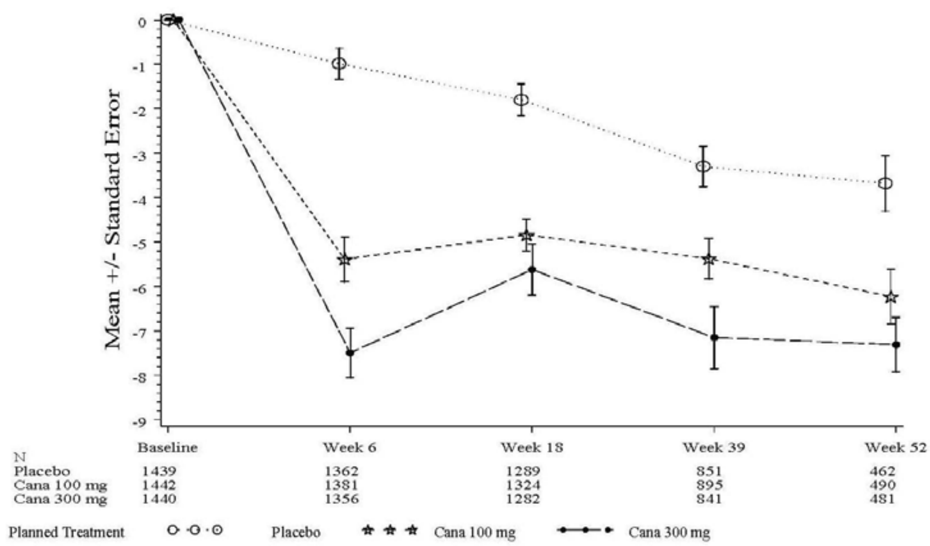


Figure 2. Mean Change (+/-SE) in eGFR from baseline in DIA3008
Source: ISS, Figure 20

With regard to the reversibility of treatment induced changes in eGFR, routine post-treatment laboratory assessments were not performed in the phase 3 diabetes studies.[1] However,

[1] In a phase 2 study in non-diabetic overweight/obese subjects (study OBE2001), laboratory values were obtained two weeks after therapy (50, 100 and 300 mg). However, when compared to placebo, no marked/clear change in eGFR from baseline to week 12 was seen on therapy in the treatment arms (mean change [SD] of 0.3 [13.6] on placebo, -1.0 [11.3] on 50 mg QD, -1.8 [14.6] on 100 mg QD and 0.8 [12.8] on 300 mg QD).

reductions in systolic and diastolic blood pressure were observed in phase 3 trials, providing support for a hemodynamically mediated drug effect on eGFR. Moreover, in studies where urine albumin/creatinine ratios were measured, there appeared to be a slight reduction from baseline in urine albumin to creatinine ratios in the canagliflozin as compared to the placebo arm (see appendix for both).

To further explore the potential clinical significance of canagliflozin's effect on eGFR, the applicant examined treatment effects on the incidence of more marked changes in eGFR (arbitrarily defined by the applicant as an eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline or a >50% reduction from baseline). In the applicant's analysis of the placebo-controlled trials dataset, the incidence of these events appeared to be similar in the 100 mg dose and placebo treatment arms, and greater in the 300 mg dose group. In contrast, in analyses of subjects with moderate renal impairment, the incidence of more marked changes in renal function appeared to be greater in both the 100 mg and 300 mg groups when compared to the placebo group. Consistent with analyses of mean effects, the Kaplan-Meir plot of time to first eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline showed an early separation of curves.

Table 2. Number of subjects with eGFR values below specified limits

	Placebo n (%)	Canagliflozin 100 mg n (%)	Canagliflozin 300 mg n (%)
Phase 3 Placebo-Controlled Studies Dataset			
	624	809	805
eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline	13 (2.1)	16 (2.0)	33 (4.1)
eGFR decrease >50% from baseline	1 (0.2)	0	1 (0.1)
Phase 3 Moderate Renal Impairment Dataset			
	367	332	352
eGFR <80 mL/min/1.73m^2 and >30% reduction from baseline	18 (4.9)	31 (9.3)	43 (12.2)
eGFR decrease >50% from baseline	0	5 (1.5)	3 (0.9)

Sources: ISS Tables 133 and 134. Any post-baseline value; percentages calculated with the number of subjects per time interval as denominator.

The incidence of renal related adverse events and renal-related adverse events leading to discontinuation was also compared across treatment arms.[2] In the phase 3 placebo-controlled trials, the incidence of renal-related adverse events and renal-related adverse events leading to discontinuations was low, though appeared to be slightly greater in the canagliflozin 300 mg dose group compared to the placebo and 100 mg dose groups. In the moderate renal impairment dataset, the incidence of these events was higher than that seen in the placebo-

[2] No systematic approach appears to have been taken to ensure the capture of renal-related adverse events in the phase 3 trials. The applicant identified potential renal-related adverse events from the larger pool of investigator reported adverse events using the SMQ for acute renal failure adverse events and a broader list of "renal related adverse events" (this list included terms under the SMQ for acute renal failure and the terms blood creatinine increased and glomerular filtration decreased).

controlled studies dataset. The incidence was also greater in both the 100 mg and 300 mg dose groups, when compared to placebo.

Table 3. Number (%) of subjects with at least one adverse event of the following types

	Placebo n (%)	Canagliflozin 100 mg n (%)	Canagliflozin 300 mg n (%)
Phase 3 Placebo-Controlled Studies Dataset			
	646	833	834
Any selected renal-related adverse event	4 (0.6)	5 (0.6)	14 (1.7)
Any selected renal-related adverse event leading to discontinuation	1 (0.2)	3 (0.4)	7 (0.8)
Any selected renal-related adverse event related to study drug	3 (0.5)	2 (0.2)	8 (1.0)
Any selected renal-related serious adverse events	0	1 (0.1)	0
Phase 3 Moderate Renal Impairment Dataset			
	382	338	365
Any selected renal-related adverse event	14 (3.7)	30 (8.9)	34 (9.3)
Any selected renal-related adverse event leading to discontinuation	4 (1.0)	4 (1.2)	6 (1.6)
Any selected renal-related adverse event related to study drug	10 (2.6)	10 (3.0)	20 (5.5)
Any selected renal-related serious adverse events	5 (1.3)	4 (1.2)	5 (1.4)

Sources: ISS Tables 142 and 145. Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication

In addition to the aforementioned approaches to exploring canagliflozin's renal-related risks, the applicant established a Clinical Events Committee to adjudicate in a blinded fashion the potential causal relationship between events of particular interest and study drug. Criteria for CEC adjudication were as follows[3] :

- Sustained doubling of serum creatinine from the baseline value (or ≥50 % decrease in eGFR from baseline) that occurred while the subject was on study drug. The definition of "sustained" was a repeat value occurring ≥4 weeks after the initial finding and with the subject having remained on study drug.
- Doubling in baseline serum creatinine (or ≥50% decrease in baseline eGFR) at last recorded laboratory value. A "last" value is defined as either last available value in subjects who completed the study or discontinued early, or as the last value available at the time of study cut-off date in subjects who continued in the study (and may have had follow-up values on drug after study cut-off date).
- End stage renal disease (ESRD, new or worsening) or renal replacement (dialysis or transplant). The CEC Charter contains terms used to search the clinical and safety databases to identify potential ESRD and/or renal replacement cases to be adjudicated

[3] According the applicant, cases were identified by review of reported local laboratory values (e.g., during hospitalization) from the sponsor's Global Medical Safety database by searching for absolute values of serum creatinine ≥ 1.2 mg/dL and/or eGFR < 60 mL/min/1.73m^2. The serum creatinine and eGFR absolute values identified in the safety database search were then compared with baseline values to determine if the case met adjudication criteria.

As of the 4-Month Safety Update, a total of 43 cases were identified that met the adjudication criteria and had adjudication results (15 in the control arm, 12 in the canagliflozin 100 mg arm and 16 in the canagliflozin 300 mg arm). The first table shows the criteria that the cases met by treatment arm; the second table shows the adjudication results for causation. The number of events is small and no clear differences are seen among the treatment arms.

Table 4. Summary of cases sent for Renal Clinical Events Committee Adjudication

CEC Criteria	All Non-Cana n/N (%)	Cana 100 mg n/N (%)	Cana 300 mg n/N (%)	All Cana n/N (%)
Any[a]	15/3640(0.41)	12/3092(0.39)	16/3462(0.46)	28/6554(0.43)
Sustained[b] elevation in serum creatinine	0	0	0	0
Sustained[b] decrease in eGFR	4/3640(0.11)	0	2/3462(0.06)	2/6554(0.03)
Last value elevation in serum creatinine	4/3640(0.11)	3/3092(0.10)	5/3462(0.14)	8/6554(0.12)
Last value decrease in eGFR	10/3640(0.27)	6/3092(0.19)	11/3462(0.32)	17/6554(0.26)
ESRD or renal replacement (dialysis or transplant[c])	1/3640(0.03)	4/3092(0.13)	1/3462(0.03)	5/6554(0.08)

Note: N is the total number of subjects from Phase 3 studies: DIA3002, DIA3004, DIA3005 (main study), DIA3006, DIA3008, DIA3009, DIA3010, DIA3012 and DIA3015, events for the renal adjudication in these studies up to July 1 2012 were included.

[a]Any refers to any of the CEC adjudication criteria

Source: 4-Month Safety Update Report, Table 27

Table 5. Summary of CEC Causality assessment for cases sent for CEC Adjudication

CEC Criteria Causality	All Non-Cana n/N (%)	Cana 100 mg n/N (%)	Cana 300 mg n/N (%)	All Cana n/N (%)
Any[a]				
Number of Cases[b]	15	12	16	28
Very Likely	0	0	0	0
Probable	1/3640(0.03)	1/3092(0.03)	2/3462(0.06)	3/6554(0.05)
Possible	8/3640(0.22)	4/3092(0.13)	8/3462(0.23)	12/6554(0.18)
Doubtful	3/3640(0.08)	2/3092(0.06)	4/3462(0.12)	6/6554(0.09)
Not Related	3/3640(0.08)	5/3092(0.16)	2/3462(0.06)	7/6554(0.11)

Note: N is the total number of subjects from Phase 3 studies: DIA3002, DIA3004, DIA3005 (main study), DIA3006, DIA3008, DIA3009, DIA3010, DIA3012 and DIA3015, events for the renal adjudication in these studies up to July 1 2012 were included.

[a]Any refers to any of the CEC adjudication criteria

Source: 4-Month Safety Update Report,Table 28

Susceptible populations

As indicated in prior analyses, compared to subjects with relatively well-preserved renal function, subjects with moderate renal impairment appear to be at greater absolute risk of developing more marked changes in renal function on canagliflozin. Additional subgroup analyses were also conducted in an attempt to identify factors that might increase the risk of clinically significant changes in renal function on canagliflozin. As shown in the table below, in univariate analyses, factors associated with the most notable increase in risk included a GFR < 60, age ≥ 65, use of diuretics, and use of ACEI/ARBs (particularly in combination with a diuretic).

Table 6. Subgroup analysis of number of subjects with any post-baseline eGFR value mL/min/1.73m^2 and > 30% decrease (Broad dataset)

	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=9439				
<60	1223 (13.0%)	8.4% (32/382)	10.9% (44/405)	9.7% (76/787)	4.1% (18/436)
60 to <90	5154 (54.6%)	3.6% (61/1686)	4.9% (83/1680)	4.3% (144/3366)	3.3% (59/1788)
≥90	3055 (32.4%)	3.2% (33/1021)	6.1% (61/999)	4.7% (94/2020)	4.5% (47/1035)
Sex	N=9439				
Male	5493 (58.2%)	3.3% (59/1803)	5.9% (104/1766)	4.6% (163/3569)	3.6% (69/1924)
Female	3946 (41.8%)	5.2% (67/1289)	6.4% (84/1319)	5.8% (151/2608)	4.1% (55/1338)
Age (years)	N=9439				
<65	6509 (69.0%)	3.8% (80/2110)	5.4% (115/2114)	4.6% (195/4224)	3.9% (89/2285)
≥65	2930 (31.0%)	4.7% (46/982)	7.5% (73/971)	6.1% (119/1953)	3.6% (35/977)
Baseline HbA1c (%)	N=9434				
≤7.9	4894 (51.9%)	4.3% (67/1563)	6.0% (97/1607)	5.2% (164/3170)	3.6% (62/1724)
>7.9	4540 (48.1%)	3.9% (59/1527)	6.2% (91/1477)	5.0% (150/3004)	4.0% (62/1536)
Use of ACE/ARB	N=9439				
No	2961 (31.4%)	1.9% (18/970)	3.5% (34/969)	2.7% (52/1939)	2.9% (30/1022)
Yes	6478 (68.6%)	5.1% (108/2122)	7.3% (154/2116)	6.2% (262/4238)	4.2% (94/2240)
Use of Diuretics[c]	N=9439				
No	6118 (64.8%)	2.6% (53/2016)	4.0% (81/2009)	3.3% (134/4025)	3.2% (68/2093)
Yes	3321 (35.2%)	6.8% (73/1076)	9.9% (107/1076)	8.4% (180/2152)	4.8% (56/1169)
Use of Loop Diuretics	N=9439				
No	8717 (92.4%)	3.4% (98/2876)	5.4% (154/2835)	4.4% (252/5711)	3.5% (104/3006)
Yes	722 (7.6%)	13.0% (28/216)	13.6% (34/250)	13.3% (62/466)	7.8% (20/256)
Use of ACE/ARB and/or Diuretics	N=9439				
Not using ACE,/ARB, or diuretics	2611 (27.7%)	1.5% (13/871)	2.5% (21/850)	2.0% (34/1721)	2.7% (24/890)
ACE/ARB only	3507 (37.2%)	3.5% (40/1145)	5.2% (60/1159)	4.3% (100/2304)	3.7% (44/1203)
Diuretics only	350 (3.7%)	5.1% (5/99)	10.9% (13/119)	8.3% (18/218)	4.5% (6/132)
ACE/ARB and diuretics	2971 (31.5%)	7.0% (68/977)	9.8% (94/957)	8.4% (162/1934)	4.8% (50/1037)
Duration of Diabetes (years)	N=9439				
<10	4705 (49.8%)	3.6% (56/1536)	5.2% (78/1502)	4.4% (134/3038)	3.3% (55/1667)
≥10	4734 (51.2%)	4.5% (70/1556)	6.9% (110/1583)	5.7% (180/3139)	4.3% (69/1595)
Diabetes Complications	N=9439				
No	6312 (66.9%)	3.1% (65/2066)	4.7% (96/2032)	3.9% (161/4098)	3.3% (72/2214)
Yes	3127 (33.1%)	5.9% (61/1026)	8.7% (92/1053)	7.4% (153/2079)	5.0% (52/1048)

[a] Incidence of eGFR values outside pre-defined limit (<80 mL/min/1.73m^2 and >30% decrease from baseline).
[b] Number of subjects in the total population with the baseline characteristic.
[c] Includes both loop and non-loop diuretics.

Source: ISS, Table 138

Consult Questions

The consult requests comment from DCRP on the following:
1. Please comment on whether the data support the theory that observed changes in renal function were due to hypovolemia alone and fully reversible.

The data as a whole suggest the observed changes in renal function are secondary to volume depletion. Although one would expect reversibility following drug discontinuation and correction of volume depletion, the applicant has not provided data that speak to the long term renal consequences of extended exposure to the drug in the proposed population (see also response to question 2).

2. Please comment on the potential clinical impact these changes in renal function may have in a population of patients with diabetes with normal renal function and in a population of patients with diabetes and moderate renal impairment.

The long term renal consequences of canagliflozin's effect on eGFR are unknown. Given the available data, including the experience with other drugs that cause volume depletion, it seems prudent to assume that the volume depletion and corresponding reduction in eGFR caused by canagliflozin places patients at increased risk for clinically significant episodes of acute kidney injury (AKI) and that larger treatment effects on eGFR will translate into greater risk.

The analyses conducted by the applicant show a relatively low absolute incidence of more marked changes in eGFR on canagliflozin in subjects with normal and "near normal" levels of renal function. Thus, the incidence of clinically important adverse renal events may be low in patients with diabetes and normal renal function (assuming other similar characteristics to the study population). However, to get a better understanding of the nature of the treatment effect on eGFR in this population (and also other populations), you might want to consider comparing the distribution of the change from baseline in eGFR across treatment arms.

The amount of safety data in subjects with diabetes and moderate renal impairment is limited (particularly in subjects with an eGFR< 45 mL/min/1.73m^2) and what data exist suggest a high absolute risk of potentially clinically meaningful episodes of AKI at both doses and, in particular, at the high dose. This risk may be related to the presence of underlying renal disease, age, concomitant therapies commonly used in this population (such as diuretics), or a combination of these and possibly other factors. In addition, this risk may be magnified in the postmarketing setting when canagliflozin is used outside the carefully monitored setting of a clinical trial and in a less selected population. Given these issues, we think considerable uncertainty remains regarding renal safety in patients with diabetes and moderate renal impairment.

3. Please comment on whether differences in changes in renal function observed between the lower and higher dose of canagliflozin (i.e., 100 mg and 300 mg) supports the notion that the 100 mg dose is safer from a renal standpoint in subjects with moderate renal impairment.

Considering the relatively high incidence of >30% reductions from baseline in eGFR in patients with moderate renal impairment and the higher incidence of these reductions at the 300 mg as compared to the 100 mg dose, it is reasonable to think that the 100 mg dose might be safer from a renal standpoint in patients with diabetes and moderate renal impairment. (See also response to Question 2).

4. Please provide comments on the significance of the observed imbalance in adjudicated renal adverse events.

Based on the 4-Month Safety Update, there does not appear to be an imbalance in adjudicated events. The small number of events in each of the treatment arms is not unexpected given the population that was studied as well as the relatively short duration of many of these studies. The results indicate that in the population that was studied and over the time span of these studies, canagliflozin did not cause a marked or obvious increase in the rate of these events.

5. If it is not possible to address some of the comments above from the data in the NDA please comment on the type of study (ies) that would be needed to resolve these issues.

The ongoing study in patients with moderate renal impairment may provide further insight into safety in this population, though the trial may not be of sufficient duration to inform our understanding of the drug's long/longer-term effects on renal function. Given its longer duration, the applicant's cardiovascular outcome trial is likely to provide more insight into long term treatment effects on renal function. In both of these studies, it will be important to obtain creatinine measurements post treatment and at a time when any effects on volume status are likely to be resolved.

Appendix

Table 7. Mean change from baseline in blood pressure*

	Phase 3 Placebo Controlled Trials	Study 3004	Study 3008
Systolic Blood Pressure			
Placebo	-0.1 (11.8)	0.2 (14.8)	-1.6 (14.2)
Canagliflozin 100 mg	-3.9 (12.1)	-5.0 (14.4)	-4.3 (14.5)
Canagliflozin 300 mg	-5.3 (12.3)	-5.9 (12.6)	-6.3 (14.4)
Diastolic Blood Pressure			
Placebo	-0.3 (7.7)	-0.6 (7.3)	-1.1 (9.1)
Canagliflozin 100 mg	-2.1 (7.8)	-1.0 (8.3)	-2.4 (8.4)
Canagliflozin 300 mg	-2.5 (7.9)	-3.7 (7.3)	-3.4 (9.1)

Sources: CSR for 3004, Table 48; CSR for 3008, Table 32
*to Week 26 in 3004 and ISS Phase 3 Placebo-Controlled Studies Pooled and to Week 52 in 3008

Table 8. Urine albumin/creatinine ratio (g/mol): mean and median change from baseline to endpoint-within 2 days after the last dose of study drug

Lab Test Panel: First Morning Void				
DIA3004- Week 26	Placebo	CANA 100 mg	CANA 300 mg	CANA Total
N	63	61	62	123
Mean baseline	29.14	28.93	25.06	26.98
Mean change (SD)	-1.43 (39.241)	-13.42 (38.753)	-9.44 (38.877)	-11.42 (38.708)
Median change	-0.07	-0.85	-0.47	-0.49
DIA3005 – Week 26	Placebo	CANA 100 mg	CANA 300 mg	CANA Total
N	149	158	154	312
Mean baseline	2.39	2.35	2.70	2.52
Mean change (SD)	1.10 (13.975)	-0.65 (6.138)	-0.38 (6.723)	-0.52 (6.425)
Median change	0.05	0.01	-0.05	-0.02
DIA3008 – Week 52	Placebo	CANA 100 mg	CANA 300 mg	CANA Total
N	432	465	445	910
Mean baseline	11.50	7.04	8.99	7.99
Mean change (SD)	1.22 (23.734)	-0.64 (20.754)	-3.19 (18.802)	-1.89 (19.854)
Median change	0.09	-0.04	-0.11	-0.07
DIA3009 – Week 52	Glimepiride	CANA 100 mg	CANA 300 mg	CANA Total
N	369	378	362	740
Mean baseline	3.70	2.60	4.27	3.42
Mean change (SD)	0.79 (15.603)	-0.15 (4.843)	-1.22 (8.276)	-0.67 (6.761)
Median change	0.00	-0.01	-0.04	-0.02

Key: Cana=canagliflozin, N=total number of subjects; SD=standard deviation
Note: For each measurement, only those subjects who had both baseline and post baseline measurements were included.

Source: ISS, Table 139

/s/

ALIZA M THOMPSON
12/02/2012

NORMAN L STOCKBRIDGE
12/02/2012

Appendix 2:

Review of Bone Safety Data

Clinical Consultation
DRUP Track Correspondence No. 384

From: Stephen Voss MD, Medical Officer DRUP

Through: Theresa Kehoe MD, Medical Team Leader DRUP
Hylton Joffe MD, MMSc, Division Director DRUP

To: Division of Metabolism and Endocrinology Products:
Jena Weber, RPM
Hyon J. Kwon, PharmD, MPH, Clinical Reviewer
Jean-Marc Guettier MD, Clinical Team Leader
Mary Parks MD, Division Director

Subject: **NDA 204042, Canagliflozin – review of bone safety data**
IND: 076479
Date of consult request: October 19, 2012

Background:
Canagliflozin (JNJ-28431754, Janssen Research and Development) is an NME oral agent for treatment of type 2 diabetes mellitus (T2DM). Canagliflozin is an inhibitor of SGLT2 (sodium-dependent glucose co-transporter 2), the major transporter responsible for renal glucose reabsorption. This inhibition results in urinary glucose excretion with reduction in plasma glucose, and potentially other benefits including reduction in body weight and fat mass, and changes in lipids. DMEP is currently evaluating NDA 204042 for canagliflozin which, if approved, would be the first in the SGLT2 inhibitor class. The PDUFA goal date is March 31, 2013.

Canagliflozin and dapagliflozin, another SGLT2 inhibitor, have demonstrated efficacy in reducing $HgbA_{1c}$, fasting and postprandial glucose, when given as monotherapy or in combination with other agents. These drugs induce an osmotic diuresis. Clinical trials of canagliflozin showed an increase in adverse reactions potentially related to volume depletion e.g. postural dizziness, orthostatic hypotension. Events of renal impairment or failure were more common in subjects with baseline moderate renal impairment or age over 65. In combination with insulin or sulfonylureas (SUs), there was an increased rate of episodes of hypoglycemia.

Bone safety has been evaluated with these SGLT2 inhibitors because of properties that may include altered renal tubule reabsorption of calcium and phosphorus, potential for altered vitamin D metabolism, tendency for weight loss, and preclinical bone findings of hyperostosis in rats with these drugs; as well as an apparent increased propensity of some diabetics for osteoporosis and/or falls (e.g. related to decreased vision, neuropathy etc.) and previous findings of increased fractures with PPARγ drugs, which may potentially be co-administered to treat T2DM.

DRUP has previously provided consultation regarding data on dapagliflozin (see consult review by Dr. M. Whitaker in DARRTS, NDA 202293, 7/18/11). Key findings of this evaluation included:

- There were no clinically significant changes in mineral metabolism (serum and urine Ca, Phos, Mg, 25-OH-vitamin D showed minimal change, PTH showed a slight increase)
- Bone turnover markers showed small inconsistent changes in bone resorption and formation
- Bone mineral density (BMD): the drug had minimal effect on mean BMD although there were outliers with positive and negative changes of ~8-12%
- The overall fracture rate was low (1.4%) and balanced between dapagliflozin and control groups
- A study of patients with moderate renal dysfunction (eGFR 30-59 mL/min) showed an apparent increase in fractures of various types with the drug, however there was no increase when subjects across all phase 2b/3 studies with moderate renal dysfunction were pooled
- Fractures were associated with various risks for falls e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state
- Dapagliflozin was associated with increased rates of hypoglycemia, hypotension, dizziness, syncope and falls, though it was not possible to directly link such events to fractures

The conclusion of this evaluation was that there was no indication that dapagliflozin has a significant adverse effect on bone, though long term data were limited at that point. DRUP is now asked to evaluate similar bone-related data for canagliflozin, submitted in NDA 204042 (original submission 5/31/12). A 4 month safety update with updated data on fractures was submitted on 10/23/12 (#0008, SD-10).

Nonclinical overview:

In rat toxicology studies, a dose-dependent increase in metaphyseal trabecular bone (hyperostosis) of sternum, femur and tibia was observed with canagliflozin treatment, which was reversible upon drug discontinuation. Reduced bone size, area and strength were also seen at higher dose, associated with decreased body weight gain at this dose. Also seen in the rats were a marked dose related increase (~10- to 18-fold) in urinary calcium excretion, and reductions in levels of PTH, 1,25-OH-vitamin D, calcitonin and markers of bone turnover (osteocalcin, CTX-1 and DPD). Rather than representing mobilization of calcium from bone, Janssen believes the increased urinary calcium results from cross-reaction of the drug with the intestinal SGLT1 glucose transporter, causing excess carbohydrate in the gut lumen which (by unclear mechanisms) results in hyperabsorption of calcium. They believe that the hyperostosis and reductions in vitamin D, PTH and bone turnover markers are secondary to this hyperabsorption of calcium. Supporting this hypothesis are the observations that diets low in carbohydrate prevented the excess calcium excretion and hyperostosis, and dietary calcium restriction also prevented the hyperostosis. In addition, studies with labeled calcium demonstrated increased enteral absorption. Lesser increases in urinary calcium (~2-to-3-fold) occurred in dogs; hyperostosis did not occur in mice or dogs.

Reviewer comment: *Increased urinary calcium, hyperostosis and reduced 1,25-OH-vitamin D and bone turnover markers also occurred with dapagliflozin in rats. For both drugs, these findings are inconsistent with clinical studies which show increased bone resorption (CTX), without increased urinary calcium excretion.*

Overview of canagliflozin clinical trials:
The ISS presents data from 40 phase 1 studies, 3 phase 2 studies and 9 phase 3 studies. Data related to calcium, phosphorus, vitamin D, PTH and bone turnover markers were evaluated in three **phase 2** studies, each of 12 week duration and with a total of 1210 subjects. Two of these (DIA2001 and TA-7284-04) were conducted in T2DM subjects, and one (OBE2001) in nondiabetic overweight/obese subjects. (The sponsor is not currently seeking the latter indication.)

There were nine **phase 3** trials of canagliflozin in T2DM, involving a total of 10,285 Type 2 diabetic adults with inadequate control. Fracture data were captured as adverse events on supplemental eCRFs in all of these studies, which include:

- 4 **placebo-controlled** studies (**DIA3005**, **DIA3002**, **DIA3006** and **DIA3012**) which differ mainly in the subjects' background diabetic therapy (diet/exercise, metformin/SU, metformin, and metformin/pioglitazone respectively), each with 52 week duration and primary analysis at 26 weeks
- 2 **active-controlled** studies (**DIA3009**, **DIA3015**) with background regimens of metformin and metformin/SU respectively, and comparator treatments of glimepiride and sitagliptin respectively; primary analysis at 1 year
- 3 studies in **special populations**, placebo-controlled, with <u>any</u> stable background regimen (including insulin):
    - **DIA3004**: patients with **moderate renal impairment** (eGFR 30-50 mL/min/1.73 m^2); 52 week duration, primary analysis at 26 weeks
    - **DIA3008**: patients with **cardiovascular disease** or at high CV risk based on risk factors; long-term study, estimated duration 4-8 years; stratified by background therapy; the largest individual study (n=4330)
    - **DIA3010**: patients at **higher risk of fracture, i.e. older age** (55-80 y/o); 104 week duration, primary analysis at 26 weeks

Enrollment criteria of these phase 3 trials included the following:
- Inclusion: in most of the trials, inadequate glycemic control was defined as $HgbA_{1c}$ of 7.0-10.0%, and fasting plasma glucose ≥ 110 mg/dL but < 270 mg/dL
- Only adults (male or female) were enrolled, mostly defined as ≥ 18 y/o (except DIA3010)
- Renal function: eGFR ≥ 60 mL/ min/1.73 m^2 was required in most studies except DIA3004 and DIA3008, and severe renal impairment (eGFR < 30 mL/min/1.73 m^2) was an exclusion for all subjects
- Subjects with other microvascular complications e.g. neuropathy or retinopathy were not excluded

DIA3010, as the phase 3 study dedicated to bone safety with measurement of bone turnover markers and BMD, had additional enrollment criteria such that subjects were older (age 55-80 y/o) and women were ≥ 3 yrs postmenopause, with the following additional exclusions:

- Treatment with a bisphosphonate, teriparatide or denosumab within 12 months
- Osteoporosis (T-score < -2.5 at any site), unless on stable treatment with estrogen replacement, SERM or calcitonin (which were allowed as concomitant drugs)
- Treatment with systemic glucocorticoids for a total of >14 days within 3 months, or likely to require such therapy during the study
- Serum 25-OH-vitamin D level ≤ 10 ng/mL
- Hypercalcemia
- Impediments to DXA: severe scoliosis or DJD of spine, spinal fusion, spine or hip implant
- Non-healed fracture, or any fracture within 12 months
- Bone metabolic disease e.g. Paget's, osteomalacia, osteopetrosis, osteogenesis imperfecta, elevation of alkaline phosphatase > 1.5 x WNL
- Rheumatoid arthritis

Demographics of these nine phase 3 studies reflects a combination of 6 studies enrolling all adults with T2DM, with mean ages of 56-58 y/o; and 3 studies involving the renal, cardiovascular and bone-safety populations, with mean ages of 69, 63 and 63 y/o respectively. Among the 9439 subjects in the long-term DS4 dataset representing 92% of phase 3 subjects, the median age at enrollment was 60 y/o, and 58% are men; 36% are enrolled in North America and 27% in Europe; 73% are white, 16% Asian and 4% black or African-American; ethnicity is 16% Hispanic. The mean BMI was 31.9 kg/m^2. The mean duration of diabetes was 9.6 years at baseline, and mean $HgbA_{1c}$ was 8.0%. At baseline, 75% of subjects were using metformin, 20% were using a sulfonylurea (SU) and 15% were using a PPARγ agent. Moderate renal impairment (< 60 $mL/min/1.73m^2$) was present in 13%. Less than 1% used estrogens.

All of these phase 3 studies are randomized, controlled, and double blinded. Each trial uses both of the canagliflozin (referred to as "Cana" in this review) doses intended for marketing, i.e. 100 mg and 300 mg daily, in addition to placebo and/or active control (collectively referred to as "Non-Cana"), except for DIA3015 which only uses 300 mg. Investigators and patients are instructed not to alter the background diabetic regimen unless the patient meets specific criteria related to glycemic control ("rescue therapy") or medication intolerance.

Bone safety assessments of canagliflozin studies include data related to calcium/ phosphorus/ vitamin D metabolism; markers of bone turnover; bone mineral density; and fractures.

Calcium metabolism

In the 12-week phase 2 dose-finding trial DIA2001 in T2DM subjects suboptimally controlled with metformin, there were no consistent Cana-associated changes in serum or urine calcium or serum phosphorus, and slight decreases in 25-OH-vitamin D and 1,25-

OH-vitamin D levels at higher doses. (see table below) There was a small, non-dose-dependent increase in PTH at week 3 in the Cana groups relative to placebo and sitagliptin, which returned to baseline by weeks 6 and 12 (in contrast to the reduction in PTH seen in the rats). Serum magnesium levels increased by ~10%. In two other 12-week phase 2 studies (OBE2001 and TA-7284-04) there were small increases from baseline in urine and serum phosphorus respectively, but also no change in serum or urine calcium. In TA-7284-04 there were also small decreases in 1,25-OH-vitamin D levels at week 8 which returned toward normal by week 12.

Study DIA2001 (Phase 2): Calcium-related metabolism

Table 153 Calcium, Calcium Regulating Hormones and Bone Turnover Markers: Mean Percentage Changes from Baseline to Week 12 (Study 28431754-DIA2001: Safety Analysis Set)

	PBO (N=65)	50 QD (N=64)	100 QD (N=64)	200 QD (N=65)	300 QD (N=64)	300 BID (N=64)	Sita (N=65)
Blood 1,25-Dihydroxy Vitamin D (Pmol/L)							
Mean baseline	124.4	119.5	131.4	131.4	129.1	124.6	134.3
Mean % change (SD)	-2.0 (43.5)	10.5 (59.0)	-9.3 (35.0)	-6.9 (40.4)	-16.3 (40.3)	-12.0 (42.4)	-5.0 (57.7)
Median % change	-13.3	2.6	-13.6	-11.2	-24.0	-18.0	-21.1
Blood 25-Hydroxy Vitamin D (Nmol/L)							
Mean baseline	68.2	59.1	60.2	60.6	64.8	62.3	64.1
Mean % change (SD)	-3.8 (35.8)	0.3 (37.0)	-1.7 (28.7)	-1.9 (38.9)	-9.1 (31.8)	-4.8 (30.0)	1.4 (56.9)
Median % change	-11.4	-7.0	-7.5	-8.9	-11.7	-13.4	-13.1
Blood Calcium (Mmol/L)							
Mean baseline	2.406	2.414	2.431	2.398	2.425	2.439	2.422
Mean % change (SD)	0.7 (4.5)	-0.4 (7.2)	-0.3 (3.6)	1.0 (5.4)	0.6 (4.4)	0.9 (5.2)	-0.2 (3.1)
Median % change	1.0	-0.2	0.0	0.6	0.0	0.4	-0.2
Blood Collagen Type 1 Beta Carboxy Telopeptide (Ng/Ml)							
Mean baseline	0.3500	0.3605	0.3381	0.3226	0.3218	0.3634	0.3424
Mean % change (SD)	9.2 (23.6)	22.5 (51.0)	29.9 (38.1)	36.6 (47.1)	35.2 (50.1)	35.0 (40.9)	3.3 (30.1)
Median % change	2.4	7.3	22.7	29.5	28.5	35.6	0.0
Blood Parathyroid Hormone (Pmol/L)							
Mean baseline	4.12	4.37	4.61	4.48	3.99	4.25	4.09
Mean % change (SD)	13.6 (50.6)	19.2 (49.9)	12.6 (46.4)	1.6 (37.2)	7.9 (39.3)	-1.0 (29.3)	9.5 (37.6)
Median % change	0.0	12.5	3.9	-11.4	0.0	-3.0	0.0
Blood Phosphate (Mmol/L)							
Mean baseline	1.149	1.209	1.160	1.117	1.223	1.197	1.168
Mean % change (SD)	4.7 (13.3)	-0.2 (13.6)	1.6 (12.1)	7.5 (14.0)	1.5 (14.8)	6.3 (14.1)	1.4 (12.2)
Median % change	4.0	-2.1	2.8	6.6	2.4	5.7	-0.9
Urine Calcium/Creatinine Ratio (Mg/mg)							
Mean baseline	0.1949	0.1926	0.2102	0.1794	0.2027	0.1629	0.1808
Median % change	-4.2	-4.0	0.0	21.3	9.2	22.7	8.0
Urine N-Telopeptide/Creatinine Ratio (Nmolbce/Mmol Cr)							
Mean baseline	22.99	25.09	24.90	29.75	29.45	25.23	21.18
Median % change	12.1	-1.3	31.7	1.4	22.5	11.4	-12.4

Source: ISS p. 332

Reviewer comment: *These findings are generally consistent with dapagliflozin studies, where there were minimal, clinically insignificant changes in serum calcium, phosphorus, magnesium, and 25-OH-vitamin D, and small increases in PTH that were clinically insignificant.*

In the pooled dataset of all placebo-controlled phase 3 trials (DS1), mean serum calcium levels increased minimally (0.6-1.1%) from baseline. There was a somewhat larger increase in mean serum phosphate: 3.6%, 5.1% and 1.5% increase from baseline to 26 weeks for canagliflozin 100 mg, 300 mg, and placebo groups respectively. In study DIA3010, there were increases of 8.3% and 10.8% in serum magnesium relative to placebo at 26 weeks, but minimal change in calcium or phosphorus.

In DIA3004, the phase 3 study of 272 T2DM subjects with moderate renal impairment, there were slight increases from baseline to week 26 in mean serum calcium, phosphorus and magnesium of 1.3%, 7.8% and 14.6% respectively for the larger (300 mg) Cana dose,

with lesser increases for 100 mg and no change with placebo. Mean serum PTH in this study decreased by 10.3% and 16.1% compared to placebo for 100 mg and 300 mg respectively, however the Cana groups had higher levels at baseline and the differences between treatment groups were not significant statistically. There were moderate increases in 25-OH-vitamin D and slight decreases in 1,25-OH-vitamin D relative to placebo.

Bone turnover markers

In two phase 1 studies (diabetic and non-diabetic subjects), there were no changes after 2 weeks of treatment with Cana on markers of bone resorption (NTX and DPD) or formation (osteocalcin and BSAP).

In the 12-week phase 2b study DIA2001 (420 male and female T2DM subjects), as per the above Table 153, there were 22-36% increases from baseline that were apparent by week 3 and persisted in the bone resorption marker CTX, compared to 9% with placebo and 3% with sitagliptin (unlike rats which exhibited decreases in CTX). Other markers (NTX, TRACP, BSAP, osteocalcin, P1NP) did not show consistent changes. Similar increases in CTX occurred in other 12-week studies in obese, non-diabetic subjects (OBE2001) and Japanese subjects (TA-7284); the latter study also showed smaller increases in NTX, and decreases in BSAP.

In the phase 3 bone-safety study DIA3010 (total N=714), bone turnover markers were measured at baseline and after 26 weeks of treatment. Consistent with the phase 2 studies, there were LS mean increases from baseline in CTx at 26 weeks of 28.8% and 36.6% with Cana 100 mg and 300 mg respectively, compared to 11.8% with placebo – differences that were statistically significant. There were smaller, non-significant decreases in P1NP with Cana compared to placebo. (see ISS Tables 155 and 156, next page)

Table 155 Serum Collagen Type 1 Beta-Carboxy-Telopeptide (beta-CTx): Percent Change From Baseline to Week 26 - Regardless of Rescue Medication (Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Serum collagen type 1 beta-carboxy-telopeptide			
Value at Baseline (µg/L)			
N	188	211	203
Mean (SD)	0.35 (0.189)	0.35 (0.177)	0.34 (0.165)
Value at Week 26 (µg/L)			
N	188	211	203
Mean (SD)	0.36 (0.204)	0.42 (0.219)	0.44 (0.227)
% Change from Baseline			
N	188	211	203
Mean (SD)	8.6 (49.7)	25.8 (44.7)	34.0 (57.5)
LS Mean (SE)	11.8 (4.7)	28.8 (4.8)	36.6 (4.9)
Diff. (%) of LS Means (SE)(minus Placebo)		17.1 (5.0)	24.9 (5.0)
95% CI [a]		(7.3;26.9)	(15.0;34.8)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline beta-CTx.

Note: The table includes only the subjects who had both baseline and post baseline beta-CTx.

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Table 156 Serum Propeptide Amino-Term Type 1 Procollagen (P1NP): Percent Change From Baseline to Week 26 - Regardless of Rescue Medication (Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Serum propeptide amino-term type 1 procollagen			
Value at Baseline (µg/L)			
N	194	222	206
Mean (SD)	34.42 (15.695)	33.68 (17.472)	33.98 (12.703)
Value at Week 26 (µg/L)			
N	194	222	206
Mean (SD)	35.94 (22.394)	33.05 (14.498)	33.22 (12.700)
% Change from Baseline			
N	194	222	206
Mean (SD)	6.8 (58.1)	2.0 (26.0)	0.4 (23.8)
LS Mean (SE)	8.4 (3.5)	2.7 (3.6)	1.5 (3.7)
Diff. (%) of LS Means (SE)(minus Placebo)		-5.7 (3.8)	-6.9 (3.8)
95% CI [a]		(-13.1;1.7)	(-14.3;0.6)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline P1NP.

Note: The table includes only the subjects who had both baseline and post baseline P1NP.

tbs04_me_core_ref1.rtf generated by ref1.sas, 17APR2012 14:49

Source: ISS

Bone mineral density is measured in this one phase 3 study, **DIA3010**, which was designed to evaluate bone safety. As such, the study enrolled older T2DM adults (age 55-80 y/o) including females who were at least 3 years post menopause, and there were several exclusion criteria related to disorders and/or medications potentially affecting bone (bisphosphonates, teriparatide, denosumab, glucocorticoids for >2 weeks). Subjects could be on any stable regimen of oral and/or injectable antidiabetic medications for at least 3 months prior to screening, or 6 months if pioglitazone was included (rosiglitazone

was not allowed). Following stratification for baseline lumbar spine T-score category (< -1.5, ≥ -1.5) and PPARγ use, subjects were randomized 1:1:1 to receive Cana 100 mg, Cana 300 mg or placebo for 2 years. If subjects met criteria for glycemic rescue during the study, the only change in background regimen not allowed was the addition of pioglitazone or change in dose thereof.

In this study, DXA of the lumbar spine, total hip, femoral neck and forearm (1/3 radius) is conducted at weeks 26, 52 and 104. The NDA includes only the week 26 data which constitutes the primary safety endpoint. The study is ongoing and the 52-week and 104-week data will be submitted in a later report. A central DXA facility (Bioclinica Inc.) is used for instrument calibration and central interpretation of the data.

[As a secondary endpoint, BMD will also be evaluated in this study using QCT of the spine and hip at week 52, in a subset of subjects (~50 per arm), in order to assess BMD changes specific to trabecular and cortical bone, geometric properties, and material properties using finite element analysis (FEA). These data are not yet submitted.]

It was calculated that 156 subjects per treatment group in this study would exclude a decline in lumbar spine BMD of > 0.9%. This is the lower bound of the 95% CI for a 2-sided comparison, assuming a standard deviation of 4.05% (derived from literature) for percent change from baseline in LS-BMD in placebo recipients over 2 years, with type I error rate of 0.05.

A total of 716 subjects were randomized, and 88% completed the 26 week primary analysis period (91% of Cana recipients and 83% of placebo recipients). The median age was 63 y/o; 56% were male; 77% were white, 9% were Asian and 8% were black or African-American; ethnicity was 15% Hispanic. Mean BMI was 31.6 kg/m^2. At baseline, 12.2% of subjects were on a PPARγ agent. Baseline T-score was ≥ -1.5 in 77% of subjects. Only one subject (#101517) took corticosteroid therapy for greater than 14 days during the study. Seven subjects were using estrogens, and 2 were using SERMs, at baseline.

The Applicant's analysis of 26-week BMD findings from study DIA3010 at the 4 skeletal sites are summarized in the Applicant's Tables 37-40 on the following pages, taken from pp. 138-139 of the CSR. Lumbar spine BMD showed small placebo-subtracted changes from baseline of +0.2% for Cana 100 mg and -0.3% for Cana 300 mg. The 1/3 radius BMD showed small placebo-subtracted declines of -0.3% and -0.4% for Cana 100 mg and Cana 300 mg respectively. The hip findings were somewhat inconsistent and also small: placebo-subtracted increases at femoral neck (+0.3% and +0.4%) but decreases at total hip (-0.4% and -0.5%) for Cana 100 mg and 300 mg respectively. Among these various changes, the only ones to achieve statistical significance between treatment groups were those at total hip (i.e. declines).

Table 37: Lumbar Spine Measurement: Percent Change From Baseline to Week 26 - Regardless of Rescue Medication

(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Lumbar spine corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	185	206	192
Mean (SD)	1.15687 (0.195706)	1.16170 (0.182599)	1.17986 (0.198626)
Value at Week 26 (g/cm^2)			
N	185	206	192
Mean (SD)	1.15956 (0.197824)	1.16622 (0.188740)	1.17984 (0.204915)
% Change from Baseline			
N	185	206	192
Mean (SD)	0.3 (2.9)	0.4 (3.0)	-0.0 (2.9)
LS Mean (SE)	0.5 (0.3)	0.7 (0.3)	0.2 (0.3)
Diff. (%) of LS Means (SE)(minus Placebo)		0.2 (0.3)	-0.3 (0.3)
95% CI[a]		(-0.4;0.8)	(-0.9;0.3)

[a] Pairwise comparison: CIs were based on an ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Lumbar Spine Corrected BMD Measurement.

Note: The table includes only the subjects who had both baseline and post baseline Lumbar Spine Corrected BMD measurements.

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Table 38: Distal Forearm: Percent Change From Baseline to Week 26 - Regardless of Rescue Medication

(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Distal forearm corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	187	208	187
Mean (SD)	0.84697 (0.128361)	0.82073 (0.131579)	0.84375 (0.147968)
Value at Week 26 (g/cm^2)			
N	187	208	187
Mean (SD)	0.84627 (0.132586)	0.81778 (0.133452)	0.84000 (0.151366)
% Change from Baseline			
N	187	208	187
Mean (SD)	-0.1 (2.9)	-0.4 (3.1)	-0.5 (3.7)
LS Mean (SE)	-0.5 (0.3)	-0.7 (0.3)	-0.8 (0.3)
Diff. (%) of LS Means (SE)(minus Placebo)		-0.3 (0.3)	-0.4 (0.3)
95% CI[a]		(-0.9;0.4)	(-1.0;0.3)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Distal Forearm Corrected BMD measurement.

Note 1: Distal forearm: region of interest, 1/3 radius (33% radius).

Note 2: The table includes only the subjects who had both baseline and post baseline Distal Forearm Corrected BMD measurements.

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Table 39: Femoral Neck: Percent Change From Baseline to Week 26 - Regardless of Rescue Medication

(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Femoral neck corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	183	209	190
Mean (SD)	0.89590 (0.148117)	0.90451 (0.158234)	0.91705 (0.155647)
Value at Week 26 (g/cm^2)			
N	183	209	190
Mean (SD)	0.89164 (0.149695)	0.90270 (0.154215)	0.91538 (0.153458)
% Change from Baseline			
N	183	209	190
Mean (SD)	-0.5 (3.2)	-0.1 (3.3)	-0.1 (3.5)
LS Mean (SE)	-1.0 (0.3)	-0.7 (0.3)	-0.6 (0.3)
Diff. (%) of LS Means (SE)(minus Placebo)		0.3 (0.3)	0.4 (0.3)
95% CI[a]		(-0.3;1.0)	(-0.3;1.1)

[a] Pairwise comparison: CIs were based on an ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Femur Neck Corrected BMD measurement.

Note: The table includes only the subjects who had both baseline and post baseline Femoral Neck Corrected BMD measurements.

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Table 40: Total Hip: Percent Change From Percent Baseline to Week 26 - Regardless of Rescue Medication

(Study 28431754DIA3010: Safety Analysis Set)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Total hip corrected BMD measurement			
Value at Baseline (g/cm^2)			
N	183	209	190
Mean (SD)	1.03454 (0.140822)	1.04628 (0.147847)	1.05251 (0.148493)
Value at Week 26 (g/cm^2)			
N	183	209	190
Mean (SD)	1.03342 (0.142058)	1.04057 (0.146836)	1.04587 (0.148591)
% Change from Baseline			
N	183	209	190
Mean (SD)	-0.1 (1.9)	-0.5 (2.1)	-0.6 (2.1)
LS Mean (SE)	-0.5 (0.2)	-0.9 (0.2)	-1.0 (0.2)
Diff. (%) of LS Means (SE)(minus Placebo)		-0.4 (0.2)	-0.5 (0.2)
95% CI[a]		(-0.8;-0.0)	(-0.9;-0.1)

[a] Pairwise comparison: CIs were based on the ANCOVA model with treatment, sex, T-score of lumbar spine (< -1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline Total Hip Corrected BMD measurement.

Note: The table includes only the subjects who had both baseline and post baseline Total Hip Corrected BMD measurements.

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Source: DIA3010 CSR

Population subgroups of gender, age group and baseline eGFR for lumbar spine BMD were prespecified. (see table) In each subgroup, changes from baseline and relative to placebo for both Cana groups were small and not statistically significant.

Study DIA3010: Lumbar Spine BMD, percent changes at week 26 by subgroups

	Placebo	Cana 100 mg	Cana 300 mg
Males, n	113	109	108
Baseline, g/cm^2	1.186	1.212	1.232
Week 26, mean % change	+0.10	+0.74	+0.03
Females, n	72	97	84
Baseline, g/cm^2	1.111	1.105	1.113
Week 26, mean % change	+0.45	-0.04	-0.04
Age < 65 y/o, n	114	119	121
Baseline, g/cm^2	1.141	1.157	1.159
Week 26, mean % change	+0.74	+0.52	+0.08
Age ≥ 65 y/o, n	71	87	71
Baseline, g/cm^2	1.182	1.167	1.215
Week 26, mean % change	-0.55	+0.21	-0.13
eGFR < 90, n	146	159	140
Baseline, g/cm^2	1.164	1.156	1.186
Week 26, mean % change	+0.25	+0.41	-0.02
eGFR ≥ 90, n	39	47	52
Baseline, g/cm^2	1.130	1.181	1.163
Week 26, mean % change	+0.15	+0.33	+0.04
Source: DIA3010 CSR pp. 1193-1198			

The Applicant conducted additional post-hoc analyses of the interaction of baseline eGFR and BMD changes, by eGFR tertile (≤ 69, 70-84, and >84 mL/min/1.73 m^2). (see table) None of these tertile subgroups showed a significant treatment-related difference in BMD changes at any of the 4 skeletal sites, and reduced eGFR was not associated with adverse BMD changes. (Note that baseline eGFR ≤ 50 was an exclusion criterion for this study.)

Study DIA3010: BMD, mean percent changes at week 26 by eGFR tertiles*

	Placebo	Cana 100 mg	Cana 300 mg
Lumbar spine			
eGFR < 69	+0.1	+0.9	+0.3
eGFR 70-84	+0.5	0.0	-0.4
eGFR >84	+0.1	+0.2	-0.1
Total hip			
eGFR < 69	-0.1	-0.4	-0.5
eGFR 70-84	0.0	-0.6	-0.7
eGFR >84	-0.2	-0.5	-0.7
Femoral neck			
eGFR < 69	-0.3	+0.4	+0.1
eGFR 70-84	-0.4	-0.3	+0.3
eGFR >84	-0.7	-0.4	-0.6
1/3 radius			

eGFR < 69	-0.3	-0.7	-0.6
eGFR 70-84	-0.3	-0.4	-1.1
eGFR >84	+0.4	+0.1	+0.2
* N= 241, 247 and 226 for eGFR < 69, 70-84 and > 84 tertiles respectively			

There were 12.2% of DIA3010 subjects on a PPARγ agent at baseline. As this component of therapy was to remain unchanged throughout the study, and this subgroup was small, no analysis was done for the subgroup. The use of PPARγ agents was not a significant term in the model used to analyze lumbar spine BMD.

Reviewer comment: *In summary as shown in the Applicant's table below, BMD changes over 26 weeks with canagliflozin were small and non-significant at lumbar spine and 1/3 radius. The total hip BMD decline was statistically significant relative to placebo, however these changes (-0.4% and -0.5% with Cana 100 mg and 300 mg respectively) were modest and in the opposite direction to those at femoral neck. Age and gender subgroups showed no significant differences in lumbar spine BMD changes; renal function subgroups did not differ from each other at any skeletal site. None of these BMD findings appear likely to be of significance clinically, however additional DXA data at weeks 52 and 104 will be helpful, as will QCT data.*

Summary: Percent Change from Baseline to Week 26 - Regardless of Rescue Medication for Bone Safety
(Study 28431754-DIA3010: Safety Analysis Set)

Endpoints – corrected BMD measurement % change	CANA 100 mg (Placebo-Subtracted) LS Mean (95% CI)	CANA 300 mg (Placebo-Subtracted) LS Mean (95% CI)
Lumbar spine	0.2 (-0.4; 0.8)	-0.3 (-0.9; 0.3)
Total hip	-0.4 (-0.8; 0.0)	-0.5 (-0.9; -0.1)
Femoral neck	0.3 (-0.3; 1.0)	0.4 (-0.3; 1.1)
Distal forearm	-0.3 (-0.9; 0.5)	-0.4 (-1.0; 0.3)

Note: The least squares (LS) mean is presented with associated CI based on ANCOVA models with terms for treatment, sex, T-score of lumbar spine (<-1.5 or ≥ -1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and adjusting for the baseline value as a covariate.

Fractures

Investigators gathered data on all suspected clinical fractures across all phase 2 and 3 studies using a supplemental eCRF which recorded the fracture date and history of the event, level of trauma and skeletal location. This information, including additional review of radiographic images as needed, is evaluated by an independent, treatment-blinded Fracture Adjudication Committee (FAC), consisting of experienced radiologists employed by Synarc, the imaging vendor. The FAC confirmed that a fracture had occurred and classified it by location and one of the following:

- **High Trauma Fracture**: fractures resulting from severe trauma such as motor vehicle crashes, being struck by a vehicle or other fast-moving projectile, or falls from greater than standing height (e.g. falls off a ladder or other raised surface, not including stairs)
- **Low Trauma Fracture**: fractures due to falls from standing height or less; falls on stairs, steps, or curbs; moderate trauma other than a fall (e.g. collisions with objects during normal activities); and minimal trauma other than a fall (e.g. turning over in bed)
- **Pathological Fracture**: fractures occurring in an area that is weakened by another disease process such as a tumor, metastatic cancer of the bone, infection, inherited bone disorders, etc.

- **Stress Fracture**: identifiable fractures caused by repetitive stress
- **Other Fracture**: fractures that cannot be attributable to the definitions above

Reviewer comment: *The intent of the high-trauma/ low-trauma classification, presumably, was to differentiate fractures that were unlikely to be related to any compromise in bone strength (high-trauma) from those that were likely to be so related (low-trauma). However, trauma history may be misleading in some cases. In particular, fractures of metacarpals, metatarsals and phalanges are generally considered to have no relationship to bone fragility, yet under the above definitions may have been classified as low-trauma. Conversely, many fractures associated with significant trauma occur in part because of underlying fragility. Thus in osteoporosis trials, fractures of vertebrae, hip, forearm and humerus (other than pathologic) are generally considered potentially relevant to bony integrity regardless of trauma severity, and fractures of hand, foot, skull or face are typically disregarded. Because this NDA did not include any information regarding the adjudication findings other than overall tabulations of the categories, the relevance of the trauma classifications used is unclear.*

Phase 3 safety data, including fracture data, were pooled for analysis in the ISS. Because the 9 phase 3 studies examined different diabetic populations (6 represented general T2DM, and one each represented subjects with moderate renal dysfunction, elevated CV risk, and older age/increased fracture risk), an effort was made to have each study's representation in the dataset evenly distributed ~1:1:1 between Cana 100 mg: Cana 300 mg: Non-Cana control. Thus, one study (DIA3015) without a Cana 100 mg group and a small substudy of another (DIA3005) without a control group were excluded. The Non-Cana control groups, representing placebo, glimepiride or sitagliptin depending on the study, were combined for comparison for the same reason.

Reviewer comment: *There is no evidence that glimepiride or sitagliptin have any significant effect on BMD or fractures, therefore it appears reasonable to combine these groups with placebo for the overall comparison of fractures.*

These data, from 8 of the 9 phase 3 studies, were pooled for analysis in the ISS, and fracture data are included in a long term (designated as "DS4") ADAE dataset. At the 1/31/12 cutoff date for ISS data, all 8 of these studies were ongoing, and 159 subjects with fractures had been reported. The 4 Month Safety Update extends the cutoff date to 7/1/12, by which time 44 additional subjects with fractures had been reported. As of that date, the length of exposure exceeded 6, 12, 18 and 24 months for 88%, 79%, 40% and 12% of the 10,285 phase 3 study subjects.

Both the ISS and 4-Month Safety Update include Applicant analysis of cumulative fractures from these 8 studies. These analyses are based on all fractures occurring post-randomization in this DS4 dataset, including those on treatment and for an unlimited length of time following end of treatment. Summary data from the FAC adjudications were also analyzed.

The long term DS4 ADAE dataset includes 9439 subjects, who were randomized to Cana 100 mg (N=3092), Cana 300 mg (N=3085), or Non-Cana (N=3262). The Non-Cana

(control) group treatment varies by study; overall this group represents 2412 subjects (74%) randomized to placebo; 484 subjects (15%) randomized to glimepiride (titrated to 1-8 mg) and 366 subjects (11%) randomized to sitagliptin 100 mg. The Non-Cana group is slightly larger than the two Cana groups because randomization in one study, DIA3006, was 2:2:2:1 to Cana 100 mg: Cana 300 mg: sitagliptin 100 mg: placebo, whereas in the other studies randomization was 1:1:1.

These 9439 phase 3 subjects were 58% male with mean age of 60 y/o. As noted in the following table, nearly half the subjects, and more than half the fractures, were from the largest study, DIA3008, which enrolled somewhat older subjects (mean age 63 y/o) with increased cardiovascular risk. The bone safety study, DIA3010, had fewer fractures compared to DIA3008 and DIA3009, as it is smaller and was initiated 5-8 months later. Collectively at the time of the ISS, there were 189 fracture events, in 159 subjects, reported in the DS4 dataset to have occurred following randomization, which were evenly distributed among the Cana 100 mg, Cana 300 mg and Non-Cana groups.

All phase 3* fracture events post-randomization, by study and treatment group (DS4, ISS, prior to adjudication)

Study	Population	Mean age	# subjects randomized in study	# of fracture events*	Cana 100 mg (n=3092)	Cana 300 mg N=3085)	Non-Cana** (N=3262)
DIA3005	General T2DM	56	587	6	1	4	1
DIA3002		58	469	4	0	2	2
DIA3006		56	1284	12	4	3	5*
DIA3012		57	344	3	1	1	1
DIA3009		57	1452	31	10	7	14*
DIA3004	Renal insuff	69	272	7	2	2	3
DIA3008	Cardiovascular	63	4330	116	42	36	33
DIA3010	Increased fracture risk	63	716	15	5	6	4
Total				**189**	**65**	**61**	**63***

* In the only phase 3 study not included in this dataset, DIA3015, there were 2 fractures with Cana 300 mg and 1 fracture with active control (sitagliptin).
** Non-Cana fractures represent placebo with the following exceptions: Study DIA3006 – 4 fractures occurred with sitagliptin 100 mg, and 1 fracture with placebo; Study DIA3009 – 14 fractures occurred with glimepiride
Source: ISS and DS4 ADAE dataset

Although the post-randomization fracture events in the ISS were overall about even among the treatment groups, the subject incidence was higher in the Cana groups: 58 (1.9%) and 54 (1.8%) in the Cana 100 mg and Cana 300 mg groups respectively, and 47 (1.4%) in the Non-Cana group.

Reviewer comment: *The Non-Cana group had fewer subjects with fractures, but about the same number of fracture AEs, relative to the two Cana groups. Thus, this group had more subjects (11) with multiple fracture AEs, relative to the Cana groups (8 and 6). All except two of these Non-Cana subjects had fractures of different bones on the same day, most notably a 63 y/o man with a motor vehicle accident resulting in fractures of scapula,*

clavicle and 5 ribs, each counted as a separate AE. Others included a 56 y/o man who fell from stairs resulting in fractures of R fibula and R calcaneus, and a 76 y/o man who incurred fractures of C-6 and C-7 in a motor vehicle accident. Most of the other subjects with >1 fracture, both Cana and Non-Cana, also appear to have experienced significant trauma. Therefore, it is unlikely that the treatment group difference in number of subjects with multiple fractures has any implications regarding bone fragility.

ISS fracture events adjudicated as high-trauma were approximately even across treatment groups (0.4%, 0.3% and 0.3% respectively), but low-trauma events were more common with Cana 100 mg or 300 mg (each 1.3%) relative to control (1.0%). The Applicant's ISS analysis found no statistical differences in these comparisons, nor when the Cana 100 mg and 300 mg groups were pooled together for comparison to Non-Cana.

In the 4-Month Safety Update, with 44 additional subjects with fractures, the Applicant updated these analyses (see Applicant's Table 29, next page). The additional fractures were somewhat more numerous with the test drug: 18, 16 and 10 additional subjects from the Cana 100 mg/ Cana 300 mg/ Non-Cana groups respectively. Thus, the updated difference in fracture incidence between the combined Cana groups (2.4%) and Non-Cana subjects (1.7%) approached statistical significance. As the Applicant notes, there were more dropouts in the Non-Cana groups, therefore the median duration of exposure was greater in the combined Cana groups relative to Non-Cana (73 vs. 66 weeks). Thus, the time-adjusted incidence rates of 18.11 vs. 14.16 fractures per 1000 person years of exposure for Cana and Non-Cana respectively were somewhat closer than the incidence rates not so adjusted. The treatment group differences in incidence of positively adjudicated fractures (2.2%, 2.0% and 1.6% respectively) were not statistically significant.

The rate of low trauma fractures continued, in the 4-Month Safety Update, to be numerically higher in the Cana groups (1.6% each, vs. 1.2% for Non-Cana), though this difference was not statistically significant. In a time to event analysis of all low trauma events in the Safety Update (adjudicated and otherwise), the curves of the Cana and Non-Cana treatment groups appear to separate even as early as 12 weeks. (see Applicant's Figure 2 below)

Table 29 Post Randomization Fracture Adverse Events by Fracture Type - Regardless of Use of Rescue Medication (JNJ-28431754 Four Month Safety Update: Safety Analysis Set) (DS3-LT2)

Fracture Type	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)	Cana 100 mg Minus ---All Non-Cana--- Diff[a]	95%CI[b]	Cana 300 mg Minus ---All Non-Cana--- Diff[a]	95%CI[b]	All Cana Minus ---All Non-Cana--- Diff[a]	95%CI[b]
Total no. subjects with adverse events[c]	76 (2.5)	70 (2.3)	146 (2.4)	57 (1.7)	0.7	(-0.0; 1.4)	0.5	(-0.2; 1.2)	0.6	(0.0; 1.2)
Incidence rate per 1000 person-years exposure (SE)[d]	18.65 (2.15)	17.56 (2.11)	18.11 (1.50)	14.16 (1.89)	4.5	(-1.14; 10.10)	3.4	(-2.17; 8.95)	3.9	(-0.79; 8.68)
Total no. subjects with Adjudicated Fracture Type[c]	68 (2.2)	61 (2.0)	129 (2.1)	53 (1.6)	0.6	(-0.1; 1.3)	0.4	(-0.3; 1.0)	0.5	(-0.1; 1.0)
High Trauma	15 (0.5)	12 (0.4)	27 (0.4)	11 (0.3)	0.1	(-0.2; 0.5)	0.1	(-0.3; 0.4)	0.1	(-0.2; 0.4)
Impact Unknown	1 (<0.1)	0	1 (<0.1)	0	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.0)	0.0	(-0.0; 0.1)
Low Trauma	51 (1.6)	48 (1.6)	99 (1.6)	38 (1.2)	0.5	(-0.1; 1.1)	0.4	(-0.2; 1.0)	0.4	(-0.1; 0.9)
Pathological	0	1 (<0.1)	1 (<0.1)	0	0.0	(-0.0; 0.0)	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.1)
Possible Unknown Trauma	0	1 (<0.1)	1 (<0.1)	0	0.0	(-0.0; 0.0)	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.1)
Stress	1 (<0.1)	0	1 (<0.1)	3 (<0.1)	-0.1	(-0.2; 0.1)	-0.1	(-0.2; 0.0)	-0.1	(-0.2; 0.1)
Unknown	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	-0.0	(-0.1; 0.1)	0.0	(-0.1; 0.1)	-0.0	(-0.1; 0.1)

[a] Denotes the difference in the incidence rate or the difference in proportion of subjects with the adverse event

[b] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[c] Fracture adverse events based upon a prespecified subset of preferred terms from a MedDRA query listed in the SAP.

[d] Exposure adjusted incidence rates are per 1000 person-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total person-year exposure for all safety subjects in each treatment group). SE denotes the standard error of the incidence rates defined as incidence rate divided by the square root of the total number of subjects with the adverse event - 1.

[e] Adjudicated fracture type for confirmed fractures by the FAC (note that events not confirmed as a fracture or without information available to the FAC are excluded).

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence Is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of use of rescue medication.

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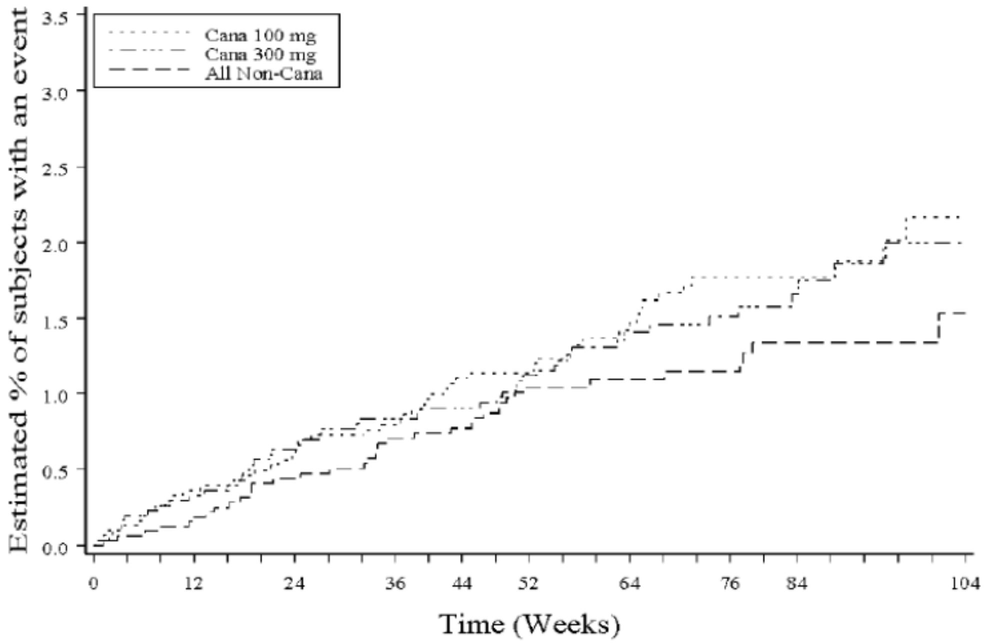
Source: 4-Month Safety Update, p. 58

Figure 2 **Kaplan-Meier Plot of Time To the First Post Randomization Low Trauma Fracture Adverse Event (JNJ-28431754 Four Month Safety Update: Safety Analysis Set) (DS3-LT2)**



No. Subjects at Risk										
Cana 100 mg	3092	3042	2983	2931	2882	2840	2021	1621	1166	421
Cana 300 mg	3085	3020	2940	2870	2844	2801	1983	1601	1125	413
All Non-Cana	3262	3192	3095	3011	2964	2877	1932	1537	1113	413

Source: 4-Month Safety Update, p. 62

The Applicant's analysis of fractures by adjudicated skeletal location and trauma category demonstrated that the treatment-group disparity is mainly confined to low-trauma upper limb fractures, and to a lesser extent spine fractures, with little difference in lower limb, pelvis or rib fractures:

Subject incidence of adjudicated post-randomization fracture events by skeletal region and trauma classification (Phase 3, 4-Month Safety Update)

Number of subjects with indicated fracture region	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total adjudicated-positive	68 (2.2)	61 (2.0)	129 (2.1)	53 (1.6)
All sites/ Low trauma	51 (1.6)	48 (1.6)	99 (1.6)	38 (1.2)
Lower limb/ All	25 (0.8)	25 (0.8)	50 (0.8)	29 (0.9)
Lower limb/ Low trauma	20 (0.6)	18 (0.6)	38 (0.6)	22 (0.7)
Upper limb/ All	**28 (0.9)**	**27 (0.9)**	**55 (0.9)**	**17 (0.5)**
Upper limb/ Low trauma	**22 (0.7)**	**22 (0.7)**	**44 (0.7)**	**11 (0.3)**
Spine/ All	7 (0.2)	2 (0.1)	9 (0.1)	2 (0.1)
Spine/ Low trauma	5 (0.2)	1 (<0.1)	6 (0.1)	0
Thoracic cage/ All	9 (0.3)	9 (0.3)	18 (0.3)	7 (0.2)
Thoracic cage/ Low trauma	5 (0.2)	7 (0.2)	12 (0.2)	5 (0.2)
Pelvis	2 (0.06)	0	2 (<0.1)	1 (<0.1)
Source: 4-Month Safety Update Tables 30 and 31				

The DS4 dataset includes all fractures, including large numbers of hand/finger and foot/toe fractures. These were somewhat more numerous in the Cana groups relative to Non-Cana: 15 vs. 3 subjects with hand/finger fractures, and 7 vs. 2 subjects with toe fractures. As noted previously, such fractures are generally recognized as having no relationship to bone fragility, as are fractures of skull, facial bones, scapula and patella; it is unclear how fractures at these sites were handled in the adjudications. Therefore this reviewer examined, from this ISS DS4 dataset, all 131 post-randomization fracture AEs involving other sites, i.e. bones with which a fracture may indicate a component of fragility, even in the context of some trauma. These included fractures of vertebrae, pelvis, ribs, clavicle, upper extremity (shoulder, humerus, radius, ulna, wrist) and lower extremity (hip, femur, tibia, fibula, ankle). As noted in the table below, the imbalance in upper extremity fractures persists, though for lower limb fractures there is the opposite i.e. a preponderance in the Non-Cana group. (NOTE: These data are from the dataset, which has no information regarding adjudications or high-trauma vs. low-trauma status.)

Subject incidence of post-randomization fractures by skeletal region, excluding non-fragility sites* (Phase 3, ISS)

Number of subjects Preferred Term	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total	**43 (1.39)**	**37 (1.20)**	**80 (1.29)**	**36 (1.10)**
Lower limb	**9 (0.29)**	**11 (0.36)**	**20 (0.32)**	**16 (0.49)**
Hip fracture	0	2	2	3
Femoral neck fracture	1	1	2	0
Tibia fracture	1	2	4	0
Fibula fracture	2	0	2	3
Ankle fracture	2	5	7	8
Lower limb fracture	3	0	3	1
Other**	1	1	2	1
Upper limb	**17 (0.55)**	**16 (0.52)**	**33 (0.53)**	**9 (0.28)**
Humerus fracture	4	7	11	2
Radius fracture	3	2	5	4
Ulna fracture	2	0	2	0
Wrist fracture	6	3	9	2
Upper limb fracture	2	4	6	1
Spine (thoracic/lumbar)	**6 (0.19)**	**1 (0.1)**	**7 (0.11)**	**1 (0.1)**
Spine (cervical, sacrum, coccyx)	2	0	2	1
Ribs/clavicle/sternum	7	10	17	7
Pelvis	1	0	1	2

Source: DS4 ADAE dataset (ISS)
* Excludes fractures of hand/fingers, foot/toes, skull, facial bones, scapula and patella
** Includes one each of Pathological fracture (verbatim = spontaneous fracture of right tibia/fibula); Fracture displacement (Distal right tibial posterior malleolar minimally); and Periprosthetic fracture (left femur periprosthetic fracture)

Reviewer comment: *The treatment difference in upper extremity fractures does not appear to be statistically significant. However even with this large number of subjects, it*

is not clear that the data have sufficient power to rule out a modest increase in these relatively infrequent events. As the Applicant notes, there is clearly no additional effect with increasing dose. Some of the fractures that appear to be increased are of types often indicative of reduced bone density, e.g. humerus, wrist and spine. Morphometric (i.e. asymptomatic) vertebral fractures, the most common manifestation of osteoporosis, were not evaluated in these studies, however it may be notable that back pain was reported by 5.1%, 5.5% and 6.4% of phase 3 subjects receiving Non-Cana, Cana 100 mg and Cana 300 mg respectively.

The above table was derived from the ISS dataset. The 4-Month Safety Update did not include an updated dataset, however did tabulate fractures by preferred term. In comparison to the ISS data in the above table, there is a net of one additional upper extremity fracture in the Cana 100 mg, no change in the Cana 300 mg, and two additional wrist fractures in the Non-Cana group, thus somewhat less disparity between the groups in upper extremity fractures.

Phase 3 subject incidence of fractures post-randomization, by skeletal site and treatment group (DS4, 4-Month Safety Update)

Preferred term	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Ankle fracture	4 (0.1)	6 (0.2)	10 (0.2)	8 (0.2)
Cervical vertebral fx	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Clavicle fracture	1 (<0.1)	2 (0.1)	3 (<0.1)	1 (<0.1)
Compression fracture	0	0	0	1 (<0.1)
Femoral neck fx	3 (0.1)	1 (<0.1)	4 (0.1)	0
Femur fracture	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Fibula fracture	2 (0.1)	0	2 (<0.1)	4 (0.1)
Foot fracture	10 (0.3)	13 (0.4)	23 (0.4)	11 (0.3)
Fracture displacement	2 (0.1)	1(<0.1)	3 (<0.1)	0
Fractured coccyx	1 (<0.1)	0	1 (<0.1)	0
Fractured sacrum	1 (<0.1)	0	1 (<0.1)	0
Hand fracture	8 (0.3)	8 (0.3)	16 (0.3)	5 (0.2)
Hip fracture	0	2 (0.1)	2 (<0.1)	2 (0.1)
Humerus fracture	3 (0.1)	7 (0.2)	10 (0.2)	2 (0.1)
Lower limb fracture	3 (0.1)	0	3 (<0.1)	1 (<0.1)
Lumbar vertebral fx	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Patella fracture	1 (<0.1)	0	1 (<0.1)	3 (0.1)
Pelvic fracture	0	0	0	1 (<0.1)
Periprosthetic fx	1 (<0.1)	0	1 (<0.1)	0
Pubis fracture	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Radius fracture	4 (0.1)	2 (0.1)	6 (0.1)	4 (0.1)
Rib fracture	7 (0.2)	10 (0.3)	17 (0.3)	8 (0.2)
Scapula fracture	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Skull fracture	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Spinal compression fx	1 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Spinal fracture	3 (0.1)	1 (<0.1)	4 (0.1)	0
Sternal fracture	4 (0.1)	0	4 (0.1)	0

Stress fracture	0	0	0	1 (<0.1)
Thoracic vertebral fx	2 (0.1)	0	2 (<0.1)	0
Tibia fracture	2 (0.1)	4 (0.1)	6 (0.1)	2 (0.1)
Ulna fracture	2 (0.1)	0	2 (<0.1)	0
Upper limb fracture	2 (0.1)	4 (0.1)	6 (0.1)	1 (<0.1)
Wrist fracture	7 (0.2)	3 (0.1)	10 (0.2)	4 (0.1)
All subjects with fracture	**76 (2.5)**	**70 (2.3)**	**146 (2.4)**	**57 (1.7)**
Source: 4-Month Safety Update, p. 58 (Table 29) and table, pp. 146-151				

To examine potential associations with fracture events in the DS4 dataset, the Applicant conducted a multivariate analysis of post-randomization low trauma fractures, applying the Andersen-Gill model. Statistically significant factors associated with an increased risk of low trauma fractures in this population include a prior history of fractures and older age. Canagliflozin treatment was not associated with an increase in low trauma fractures (hazard ratio of 1.26, 95% CI: 0.834 to 1.892, p=0.257) in this multivariate analysis:

Andersen-Gill model for the analysis of occurrences of post randomization low trauma fractures (DS4, ISS)

Variable	Coefficient	SE	Chi-square test	p-value	Hazard ratio*	HR 95% CI
Treatment group (All Cana=1, All Non-Cana=0)	0.228	0.209	1.190	0.275	1.256	0.834, 1.892
Age	0.035	0.012	9.096	0.003	1.036	1.012, 1.060
Gender (male=1, female=2)	0.278	0.541	0.264	0.607	1.320	0.457, 3.813
Baseline menopausal status (yes=1, no=0)	0.470	0.539	0.762	0.383	1.600	0.557, 4.599
Prior history of fractures (yes=1, no=0)	0.689	0.257	7.183	0.007	1.991	1.203, 3.295
* Hazard ratio > 1 indicates increased risk in subjects with larger values of the explanatory variable Source: ISS p. 2366						

PPARγ exposure: Of the 159 subjects with fractures reported in the ISS, only 3 were in subjects receiving a PPARγ as background therapy. These were: a 52 y/o female placebo subject with left foot and great toe fracture; a 62 y/o male Cana 100 mg subject with metacarpal fractures; and a 76 y/o male placebo subject with C-6 and C-7 fractures due to MVA.

Reviewer comment: *These are unlikely to be fragility-related fractures, thus it does not appear that PPARγ use had an effect on fractures in these studies.*

Gender:

Analysis by gender shows that women, who constituted 42% of phase 3 subjects, accounted for most of the upper extremity fractures, and most of the treatment imbalance

thereof. (see table) The mean age of the subjects with upper extremity fractures was 63 y/o for both men and women. The mean study day of the fracture was 234 days.

Phase 3 subject incidence of fractures post-randomization, by skeletal region and gender (DS4, 4-Month Safety Update)

	Cana 100 mg n (%)	Cana 300 mg n (%)	All Cana n (%)	All Non-Cana n (%)
Men, N	1803	1766	3569	1924
Total w/ fractures	33 (1.8)	35 (2.0)	68 (1.9)	27 (1.4)
Adjudicated pos.	28 (1.6)	31 (1.8)	59 (1.7)	26 (1.4)
Lower limb	13	13	26	17
Upper limb	7	13	20	7
Women, N	1289	1319	2608	1338
Total w/ fractures	43 (3.3)	35 (2.7)	78 (3.0)	30 (2.2)
Adjudicated pos.	40 (3.1)	30 (2.3)	70 (2.7)	27 (2.0)
Lower limb	12	12	24	12
Upper limb	21	14	35	10
Source: 4-Month Safety Update Table 32, p. 61				

The treatment imbalance in women was most notable in wrist fractures. The following table is derived from the ISS dataset therefore does not reflect either the adjudications or the 4 month safety update:

Phase 3 subject incidence of upper extremity fractures in women post-randomization (ISS)

	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total upper limb	**13**	**12**	**25**	**5**
Humerus fracture	3	6	9	2
Radius fracture	3	1	4	2
Ulna fracture	1	0	1	0
Wrist fracture	**5**	**3**	**8**	**0**
Upper limb fracture	1	2	3	1
Source: ISS dataset				

Of the upper extremity fractures in the ISS dataset, 25% occurred within 12 weeks of starting study medication and 42% within 26 weeks, and the disparity in fractures between treatment groups was apparent within the first 12 weeks, as noted above. The Applicant considered that these short time frames would be unlikely to reflect treatment-related changes in bone susceptibility to fracture (e.g. changes in BMD). Thus they investigated the possibility of other factors, in particular an increase in falls related to canagliflozin's potential for dehydration and/or volume depletion. There did appear to be increases in such symptoms as hypotension, orthostatic hypotension and postural dizziness associated with the larger (300 mg) Cana dose, especially during the first 30 days of treatment. However, the Applicant conducted a detailed review of narratives on all subjects with upper limb fractures, and did not find any to include reports of orthostatic hypotension, postural dizziness, lightheadedness, dizziness, presyncope or

syncope. Moreover, subjects with low trauma fractures did not display notable changes from baseline in hemoglobin, BUN, creatinine, systolic or diastolic blood pressure, and none were reported to have a hypoglycemic episode on the day of the fracture.

Renal Impairment

Fractures were assessed in the subset of phase 3 subjects (n=1087) with moderate renal impairment, defined as eGFR 30-59 mL/min/1.73 m^2. There were 21 fracture AEs in this group, including 17 which were positively-adjudicated, with a slight preponderance in the Cana 100 mg group:

Subject incidence of post-randomization fractures in subjects with moderate renal impairment, by skeletal region (Phase 3, 4-Month Safety Update)

	Cana 100 mg (N=339) n (%)	Cana 300 mg (N=365) n (%)	All Cana (N=704) n (%)	All Non-Cana (N=383) n (%)
Total with fracture AEs	9 (2.7)	6 (1.6)	15 (2.1)	6 (1.6)
Total positively adjudicated	9 (2.7)	4 (1.1)	13 (1.8)	4 (1.0)
Lower limb	1	2	3	2
Upper limb	3	2	5	1
Spine	3	0	3	1
Thoracic cage	1	1	2	0
Pelvis	1	0	1	0

Source: 4-Month Safety Update Table 33, p. 63

Summary and Conclusions

Canagliflozin is an NME oral agent for treatment of Type 2 diabetes, which acts through inhibition of SGLT2 in the renal tubule. This drug and a related SGLT2 inhibitor, dapagliflozin, are associated with altered calcium metabolism and hyperostosis of trabecular bone in rats. However, these drugs did not show any significant changes in calcium metabolism in clinical studies. Canagliflozin appears to cause a small increase in serum phosphorus and magnesium levels, and possibly a slight decline in 1,25-OH-vitamin D levels. In the key phase 2 study, this drug also was associated with a slight increase in PTH levels at 3 weeks, however PTH returned to baseline at 6 and 12 weeks, and phase 3 subjects with moderate renal impairment experienced a slight decline in PTH relative to placebo.

Previously, clinical trials of dapagliflozin did not show any consistent changes in bone turnover markers or bone mineral density. In contrast, canagliflozin demonstrated, in a population of 716 older adults (age 55-80, mean 63 y/o, 55% male), placebo-corrected increases from baseline in serum CTX (a marker of bone resorption) of 17% and 25% for the 100 mg and 300 mg doses respectively at 26 weeks, which were statistically significant (Study DIA3010). Serum P1NP, a marker of bone formation, showed minimal increases in the Cana groups which were less than placebo, and not significant, in this study.

The mechanism of the apparent dose-dependent increase in bone resorption is unclear. There was a mean weight loss of 2.4 kg and 3.0 kg (for 100 mg and 300 mg doses respectively) at 26 weeks in this study. Weight loss, particularly in the absence of a concomitant increase in exercise or physical activity, is typically associated with increased bone resorption and CTX levels, and decreased BMD. However, dapagliflozin resulted in weight loss comparable to canagliflozin, presumably via the same mechanisms, without a significant effect on CTX or other bone markers.

A 17-25% increase in CTX might have been expected to result in significant declines in week 26 BMD, however observed BMD changes in study DIA3010 were small and inconsistent at lumbar spine, with small decreases at 1/3 radius, and small decreases at total hip (-0.4% and -0.5%) but small increases at femoral neck (+0.3% and +0.4%). Only the decreases at total hip reached statistical significance, and the Applicant is probably correct in their conclusion that the magnitude of the BMD changes is not sufficient to have clinical significance. The additional data anticipated from this study (DXA at weeks 52 and 104, QCT at week 52 in a subset) will be required before any definitive conclusions on the effect of Cana on bone density may be reached.

An analysis of clinical fractures in nearly 10,000 phase 3 Type 2 diabetics (mean age 60 y/o, 58% male) showed apparent canagliflozin-associated increases in overall fractures (2.5%, 2.3% and 1.7% for Cana 100 mg, Cana 300 mg and control respectively); overall positively-adjudicated fractures (2.2%, 2.0% and 1.6%); positively-adjudicated low-trauma fractures (1.6%, 1.6%, and 1.2%); overall upper extremity fractures (0.9%, 0.9% and 0.5%); and positively-adjudicated low-trauma upper extremity fractures (0.7%, 0.7% and 0.3%). The imbalance appears to be most pronounced in women with wrist fractures. There is also an imbalance in adjudicated low-trauma spine fractures (5, 1 and 0 for the three groups). These fracture results differ from those of the related drug dapagliflozin which was not associated with an overall increase in fractures. Conversely, studies of subjects with moderate renal impairment showed a dose-related increase in fractures with dapagliflozin, but not canagliflozin.

There are several factors to consider in interpreting these fracture results. The treatment group comparisons do not reach statistical significance, except for borderline-significance of the overall (prior to adjudication, and without regard to trauma) fractures at all sites combined. However, the phase 3 program was not specifically powered to rule out an increase in fractures, which are relatively infrequent even in a sample population of 10,000. Canagliflozin was associated with increased upper extremity fractures relative to control, however lower limb fractures display somewhat of the opposite trend, and there are no apparent dosage effects between 100 mg and 300 mg in any category of fractures. There are fewer phase 3 dropouts with Cana relative to control, thus somewhat greater mean observation time for detection of fractures. The Applicant notes that the treatment imbalance in low-trauma fractures is apparent within 12 weeks of treatment and that there is a dose related increase in events of postural dizziness and orthostatic hypotension, though it is unclear whether these help to explain the fracture findings.

In summary, clinical trials of canagliflozin demonstrate a modest dose dependent increase in bone resorption, which may contribute to bone fragility. There is also a potential increase in fractures, however the latter is apparent within 12-26 weeks of treatment, during which time frame there is no apparent decline in bone density sufficient to provide plausibility for this mechanism. The potential excess in fractures was essentially limited to the upper extremity, which would be highly unusual for a bone fragility issue. This suggests that falls may be a factor, though the information submitted is not sufficient to reach any conclusions about this. Further data on BMD and fractures will be forthcoming and will be needed to determine if there is a safety signal for fractures.

Labeling

The Applicant has not proposed any labeling content related to any of the bone-related data with the exception of the following statement in section 14.3 Studies in Special Populations/ Study in Older Patients, referring to week-26 DXA data from study DIA3010:

> *There were no meaningful changes in bone density in trabecular and cortical regions.*

DRUP Recommendations

1. The above-noted proposed labeling statement should be modified to:
   There were no meaningful changes in bone density <u>through week 26</u>. Specifying cortical and trabecular BMD is not warranted.
2. We do not believe that the fracture data warrant any labeling at this time. However, we would defer to DMEP regarding this issue. In any case, it will be important to re-evaluate the bone data at the conclusion of study DIA3010, when the additional DXA data (weeks 52 and 104) are available. Updated fracture data should also be re-evaluated at that time, including fractures through the conclusion of study DIA3010 and fractures reported up to that time in study DIA3008. This information should include narratives of all (cumulative) reported fracture events and the adjudication decisions made regarding each one. We recommend making these trials PMRs, to assure that the additional bone data are submitted in a timely manner. DRUP would like the opportunity to review the additional data.
3. Based on current data, it is acceptable to not include the bone marker data (CTX) in labeling, as there is no evidence that it has clinical significance. However, if updated fracture data, and/or additional DXA data (weeks 52 and 104) were to indicate a significant bone safety issue, the CTX information should be included in the added labeling.

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/s/

STEPHEN R VOSS
12/04/2012

THERESA E KEHOE
12/05/2012

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12/05/2012

Appendix 3:

Review of Cases of Liver Injury

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	12 December 2012
To:	Mary Parks, M.D., Division Director Division of Metabolic and Endocrine Products
Reviewer:	Leonard Seeff, MD, Hepatologist Office of Surveillance and Epidemiology
Through:	Allen Brinker, MD, MS, Medical Team Leader Division of Pharmacovigilance 1
Drug Name:	canagliflozin
NDA Number:	204-042
Applicant/sponsor:	Janssen
OSE RCM #:	2012-2473
Issue:	Review of a cases of liver injury in association with canagliflozin

Executive Summary

Although plagued by the common problem of missing data or a competing cause for liver injury not sought, thus creating difficulty in absolutely ruling out drug-induced liver disease (dili) or in establishing an alternative diagnosis, there is little compelling evidence in review of these cases to implicate canagliflozin as a drug clearly capable of causing dili if it occurred. There are a few instances in which this diagnosis cannot be absolutely excluded because all possible alternative diagnoses have not been excluded or data are lacking, but most of these are cases of relatively mild liver disease. The diagnoses in some of them may be resolved if the sponsor is able to produce additional information.

In sum, based on this group of cases selected for review, no signal for hepatotoxicity is appreciated for canagliflozin at this time.

Background

This review is based on a consult request for the Division of Metabolic and Endocrine Products (DMEP) dated 18 October 2012 to review selected cases of potential drug-induced liver injury (dili) in association with canagliflozin (NDA 20-4042). Canagliflozin is currently under review by the Agency as an oral agent for the treatment of DM2.

As noted in the consult request, DMEP noted a slight imbalance (against cangliflozin) in the incidence of subjects with ALT > 5X ULN and >10X ULN and in incidence of subjects meeting biochemical Hy's law in registrational trials. DMEP requests a review of selected cases by OSE's hepatology consultants including comment on the significance of the overall imbalance based on the findings from your review.

This review is organized in 3 sections (A, B, and C) based on the organization of the consult request.

Review of Cases

Part A: Request for review of two cases regarded as unlikely DILI by sponsor's Hepatic Events Assessment Committee (HEAC)

ID (b) (4)

This was a 61 year-old man with a history of type 2 diabetes, diabetic neuropathy, hypertension, osteoarthritis and arthroplasty of the right hip. He had apparently been treated with metformin for his diabetes, but the actual start date of this drug was not reported. On a background of normal baseline liver chemistries (ALT, AST, ALP, Bilirubin, GGT), he was started on treatment with canagliflozin on March 31, 2010. Over the course of the following year and a half, liver panel testing was performed at approximately 3 month intervals and remained completely normal until June 31, 2011 (approximately 15 months after starting treatment with canagliflozin). The next series of tests were performed on September 8, 2011 with results that are disputed. Apparently,

another patient was seen at the same site and same day 10 minutes after the present subject, and had blood drawn that was found to have markedly elevated liver tests (the actual values not reported). The sponsor believes that the test results were switched between the two subjects and that the present subject in fact had quite normal chemistries. The information presented is, however, somewhat confusing. Blood drawn 3 weeks later from the present patient (September 27, 2011, now about 18 months after starting the drug) revealed obviously abnormal liver chemistries (ALT 905 IU/L; AST 478 IU/L; alp 123 IU/L. Bilirubin 2.0 mg/dl; and GGT 697 IU/L). That this was not a transient finding is evident by the fact that in three subsequent blood draws, similar abnormalities were found although slowly improving. The last set of values shown, on October 17, 2011, 20 days after the first reported abnormalities, displayed values that were still abnormal (ALT 195 IU/L; AST 60 IU/L; Alp 98 IU/l, Bilirubin, 1.1 mg/dL, and GGT 370 IU/L).

The precise cause of the abnormal liver chemistries is unclear. It is almost certainly not a consequence of treatment with canagliflozin because of the latency of 18 months from start of drug even though improvement occurred with withdrawal; however, improvement was apparent even before drug withdrawal. Serologic tests for hepatitis A and B excluded these two conditions. The patient is reported to be positive for anti-HCV but the test for HCV PCR is pending as are the tests for ANA and EBV. The patient was started on treatment with pioglitazone September 8, 2011 that was terminated on October 2, 2011 by which time, the enzyme values had already begun to decline.

Comment: Canagliflozin hepatotoxicity is almost certainly ruled out as a cause because of the 18 month latency and the fact that the enzyme levels began to decline even before withdrawal of the drug. The subject did develop late in follow-up what appears to be acute hepatocellular liver injury with hyperbilirubinemia but without jaundice. The cause for the liver injury is unclear. The timing of the start and stop dates of pioglitazone relative to the identified liver injury makes liver injury from this drug highly unlikely. Not ruled out are infection from hepatitis C and E. A positive test for either would provide useful information to help resolve the diagnosis.

ID (b) (4)

This request represents a case that has been reviewed several times in the past by this reviewer and Dr. John Senior during which times no definitive diagnosis for the observed liver dysfunction could be reached for this case. The view on each of these occasions was that the available data were insufficient to achieve a diagnosis of what appeared to be a cholestatic form of liver disease that developed about 8 months after starting treatment with canagliflozin. The last set of data reported at the time was from October 19, 2011. A review was submitted in November 2012.[1]

The sponsor has now submitted additional work-up data, providing information to as recently as mid-July, 2012.

Briefly, this was a man in his late 60's who had participated in a double-blind, placebo-controlled trial and who was admitted to hospital with abdominal pains, chills, nausea and vomiting approximately 8 months after starting the trial. He had been in the treatment arm that received canagliflozin. The patient had also been on multiple other drugs for his diabetes, hypertension, coronary artery disease, and gastro-esophageal reflux. His liver chemistries showed moderate increases in his aminotransferases and alkaline phosphatase as well as a significant increase in his serum bilirubin value. In general, the pattern of injury suggested cholestatic liver disease and biliary tree disease was suspected but initial evaluation was unable to prove this diagnosis. An ultrasound scan and magnetic resonance cholangiopancreatography of the upper abdomen was unrevealing. Noteworthy is that despite discontinuing canagliflozin, the abnormal chemistries persisted. Despite the fact that he had been evaluated at two different hospitals, the diagnosis remained unclear. Indeed, a liver biopsy that was considered worth performing was cancelled because the liver chemistries showed improvement, yet the serum enzymes and serum bilirubin still remained elevated, although at a lower level. He continued to complain of severe pruritus. Drug-induced liver injury remained suspect

[1] John Senior and Leonard Seeff to Mary Parks. Possible hepatic adverse effects of canagliflozin. 28 November 2012.

but uncertainty was expressed regarding whether it was due to canagliflozin or other drugs (simvastatin, pioglitazone) although the injury pattern was atypical for these drugs.

Additional follow-up data have since revealed that he has continued to have abnormal liver chemistries with moderate increases in his aminotransferase levels, some higher increase in ALP levels and persisting modest hyperbilirubinemia. A liver biopsy was performed on November 11, 2011 and was reported to show prominent proliferative duct reaction, cholestasis and portal fibrosis, interpreted at first as displaying hepatic duct stenosis and later as a "biliary tract process." In January, 2012, he had an MRI with contrast of the abdomen that showed an "irregular intrahepatic biliary tree with moderate peripheral intrahepatic biliary dilatation and normal appearing extrahepatic bile ducts." In February, 2012, an ERCP was performed that showed several segments of mild to moderate narrowing of the intrahepatic bile ducts now raising the specter of sclerosing cholangitis. Putting this together, a hepatology consultant raised the possibility of primary biliary cirrhosis. However, as best as can be determined from the report of the liver biopsy, PBC was not raised as a possible diagnosis. Moreover, there is no report of testing for anti-mitochondrial antibody. Also of note is that the hepatologist involved felt that the manifestations in this patient were not typical for sclerosing cholangitis and that the presentation was more likely that of drug induced liver injury. In June, 2012, the patient was hospitalized because of increasing jaundice, weakness and chills attributed then to sclerosing cholangitis. He was treated with antibiotics. At this point, the possibility of performing liver transplantation was raised.

Comment: This is an extraordinary odyssey for this patient who has now had prolonged low grade jaundice that seemed to begin about 8 months after starting treatment with canagliflozin. He was taking many other drugs but there is still no information regarding start and stop dates for these drugs. It is clear that the liver disease has shown a cholestatic pattern with bouts of what appeared to have been cholangitis. It is clear also that the disease process has been advancing with the most recent consideration for performing a liver transplantation although I don't see definitive evidence of end-stage liver disease. I believe that the features of this illness are consistent with sclerosing

cholangitis. This, of course, raises the question of whether canagliflozin might have been the precipitating event. Three sets of liver chemistries following the beginning of treatment with canagliflozin were normal, which might suggest that the drug could have played a role. However, it is not atypical for sclerosing cholangitis to have sporadic liver dysfunction early in its course so that, in my view, these normal values do not exclude a diagnosis of "idiopathic" sclerosing cholangitis, which represents my current diagnosis. I cannot entirely exclude the possibility that canagliflozin did play a role in inducing this liver disease, but I would grade it as an extremely low possibility.

Part B: Request to review two phase 3 development cases with jaundice

ID 2062301

Minimal information is provided for this case that involved a 64 year-old man who developed deep jaundice, moderately elevated aminotransferase levels and markedly elevated alkaline phosphatase levels. Little information is provided other than a final diagnosis of biliary tree cancer. The biochemical values are consistent with this diagnosis and there are no data provided to dispute this.

ID T060404

Once again, the information provided here is minimal, as evidenced in part by the fact that only one set of liver chemistries is shown. This describes a 68 year old man with DM2 who, 24 weeks after starting treatment with canagliflozin, developed abnormal liver-related chemistries (ALT 296 U/L, AST 106 U/L, ALP of 481 U/L, and a total bilirubin value of 0.7 mg/dL. No other values are shown, but an abdominal US showed intrahepatic duct dilatation, a CT scan showed pancreatic duct narrowing, retroperitoneal fibrosis and interstitial nephritis together with elevated IgG4 levels. These findings are apparently reflective of "autoimmune pancreatitis." It would, however, have been helpful to have additional laboratory values to determine which direction they were moving in, specifically to learn whether the abnormal values persisted or subsided, and whether jaundice developed. Thus, the sponsor could provide additional information and whether

any other potential diagnoses were sought. However, the available information does point to autoimmune pancreatitis.

Part C: Request to review cases of "severe hepatic enzyme elevation or liver failure" to determine agreement with the applicant's assessment of causality

There are 18 cases in this category, but many of them were either poorly evaluated for causality or provided incomplete data.

ID 500611

This 50 year old female developed a transient mild increase in ALT, AST and ALP on day 15 of treatment with immediate return to normal but followed by a more marked increase in serum enzymes with fluctuating levels thereafter until day 393, the last value shown. Bilirubin apparently remained normal throughout. The drug was discontinued just before a marked increase in the values. Tests for hepatitis A, B, and C were negative. Markers for autoimmune hepatitis were not reported. The patient did have a background of cholelithisis that conceivably could have accounted for the abnormalities. However, there is uncertainty about what the cause was for these abnormalities that seem to have persisted for 8-9 months without resolution. This reviewer does not suspect that the drug was responsible although uncertainty remains. It would be interesting to know what the sponsor's experts think about this case.

ID 150867

This 63 year old man had abnormal liver-related chemistries from the outset, although there was a sudden marked increase in the ALT, AST and ALP on day 85 lasting through day 149 without an increase in the bilirubin level. A hepatitis panel revealed that the patient had chronic hepatitis C. Accordingly, this is not an instance of drug induced liver injury.

ID 601010

This 28 year old man had evidence of necroinflammatory liver disease beginning on day 1 of treatment, so clearly this is not a case of dili. This appears to be a case of chronic hepatitis C based on the finding of anti-HCV but no test for HCV RNA is provided. It is also interesting that there is a single set of values on day 72 that are quite normal. Does this signify recovery from hepatitis C, which would be unusual?

ID 601977

This 68 year old man had abnormal liver chemistries from before and at the time of starting treatment ruling out dili as a cause for the abnormalities. Data reported are skimpy but the values, although fluctuating into the normal range, were still abnormal when the patient was last seen. Thus, this appears to be chronic necro-inflammatory liver disease but the cause is not apparent. Hepatitis serology was not reported, information that should be made available by the sponsor.

ID 602444

This was a 40 year old female who developed a single set of abnormal aminotransferase levels at week 85 of treatment that returned to normal immediately thereafter. Since the drug continued to be taken and the liver chemistries nevertheless normalized, this is not a case of dili. The reason for the single abnormality is not clear.

ID 602764

This 64 year old female with normal liver chemistries baseline was found to have moderate to marked increases in her liver chemistries beginning on day 85 (although no blood test results are reported between day 46 and day 85). The serum bilirubin value was normal. The drug was discontinued on day 87. The abnormal values gradually decreased but were still slightly abnormal on day 95, the last value shown. Hepatitis serology A, B, and C were negative as were ANA and SMA. Thus this is an acute but mild hepatitis without an obvious etiology. What needs to be determined is whether the patient developed acute hepatitis E, and the sponsor should be queried on this point. Until this is done and the results reviewed, a diagnosis of mild dili cannot be ruled out. Indeed, this

could be a possible to probable dili, a diagnosis that would be reversed if testing supported a diagnosis of acute hepatitis E virus infection.

ID 602830

This 35 year old woman with normal baseline liver chemistries was found to have mild increases in her ALT levels beginning on day 85 increasing by day 179, although no values are shown for the period between day 121 and day 179. Thereafter, the values remained abnormal up to the time of the last set of values tested, on day 310. The drug was withdrawn on day 277. This appears to be an instance of chronic necro-inflammatory disease with an undetermined etiology. This could conceivably be a case of acute progressing to chronic hepatitis C, but no serology for any of the hepatitis viruses was reported. Until then, dili cannot be ruled out as a cause for the liver injury that could be graded as at least possible and perhaps even probable.

ID (b) (4)

This 66 year old man has cryptogenic cirrhosis without evidence of dili.

ID (b) (4)

This 64 year old man developed a lymphoproliferative disorder and apparent cholecystitis with septicemia that was apparently responsible for his death. He did not develop dili.

ID (b) (4)

This 61 year old man developed an acute hepatitis on day 282 of treatment that was diagnosed as acute hepatitis E. He was also found to have a hepatic cyst. There is no evidence of dili.

ID (b) (4)

This was a very well worked up case involving a 66 year old man who developed abnormal serum enzymes and quite deep jaundice on day 237 of treatment. The enzymes have remained normal although fluctuating until day 412 at a slightly lower level. Treatment was discontinued on day 239. The bilirubin level was still abnormal on day

412 although also reduced. All hepatitis serology, including for hepatitis E as well as for autoimmune hepatitis, were negative, as was the test for CMV. However, one of the tests for EBV was positive. The latency in this case was prolonged beyond that consistent with dili, but still the diagnosis in this case is unclear to me. There was a slight suggestion that the patient had cholecystitis. Dili cannot be completely ruled out as a diagnosis. Further information from the sponsor would be desirable.

ID (b) (4)

This was a 68 year old man whose liver chemistries remained normal until day 131 of treatment. The next test reported was on day 275, a huge gap from the prior test that displayed an ALT value of 302 and an AST of 95. That was the last value shown. The patient withdrew consent for further treatment on day 274. No information can be expected. A diagnosis of dili is unlikely given the long latency.

ID (b) (4)

Minimal information supplied regarding this 68 year old woman who developed modestly elevated ALT, AST and ALP values on day 260 of treatment that fell almost to normal one week later. This represents latency generally beyond that of dili, but the cause is unclear. One suggestion is that EBV infection might have played a role. It would be useful to obtain further follow-up information on this case.

ID (b) (4)

This is an absolutely inexplicable case. This 63 year old woman had completely normal liver chemistries except for a dramatic increase of the ALT to 2075 U/L, the AST to 3969 U/L, with normal ALP and bilirubin values on day 41 of treatment. The values immediately thereafter are normal and the patient had no symptoms. The sponsor believes that there was a mix up in samples or there was something amiss with the testing. I concur and believe this is not dili.

ID (b) (4)

Once again, the information supplied here is somewhat skimpy. This was a 75 year old man started on treatment with canagliflozin who had normal liver chemistries; unfortunately, there were only a small number of test results reported. On day 285 of treatment, he developed vomiting and diarrhea, and was found to have moderate elevations of his aminotransferase levels. His bilrubin and ALP values remained normal. The drug was discontinued 3 days later. He was found to have diabetic ketoacidosis for which he was successfully treated. The serum enzyme levels normalized fairly rapidly and were back to normal by day 301. Serologic tests for hepatitis A, B, and C were non-reactive and US evaluation suggested the presence of a small gallstone or polyp. The precise cause for the transient but relatively mild increases in the serum enzymes remains uncertain. Were it not for the fact that this would represent an unusually prolonged latency between start of treatment and onset of liver injury, this could be considered a possible instance of dili.

ID (b) (4)

This 63 year old woman had mildly abnormal aminotransferase levels at the beginning of treatment that returned to normal on day 85 and then increased considerably when next tested on day 183 (why no tests in the interim?). The few tests obtained thereafter showed improvement but still abnormal values up to the last test reported. The drug was withdrawn on day 223 over a month after the increased values were found and after the values had begun to decline, suggesting that the drug was not responsible for the injury. This patient appears to have chronic liver disease from the outset but surprisingly, the only hepatitis serology reported was that of hepatitis A. Accordingly, chronic hepatitis B and C, and of course autoimmune hepatitis, are not ruled out as potential etiologies. A major problem in this case is that there are relatively few results of liver-related tests reported and that they are far-spaced. There is uncertainty in whether or not this is dili but the possibility is quite low. More information from the sponsor would be helpful in determining the etiology of the liver dysfunction.

ID (b) (4)

This 56 year old man had fluctuating abnormal aminotransferase levels from the beginning of treatment through to the last value shown, on day 515. During this period, the study drug was interrupted for relatively short periods and finally withdrawn on day 473. Because values were abnormal from the outset, this is not a case of dili but the actual cause for the abnormalities remains unclear. His hepatitis serology (A, B, C) and autoimmune serology were non-reactive, but there is a hint of EBV infection. The sponsor believes that the abnormalities were due to steatosis but the criteria for this diagnosis are quite spotty.

ID (b) (4)

As is the case for many of these reports, the data presented are meager. This was a 59 year old woman with normal baseline liver chemistries who was found to have raised values for ALT, AST and bilirubin on day 98 of treatment; however, no values are reported between the baseline testing and day 98. The next tests were reported from day 104 which showed a decline in the abnormal chemistries. Shortly thereafter, the drug was withdrawn (values has already begun to decline prior to this) and the last value shown, on day 116, was still abnormal although less so. Testing for hepatitis B and C showed negative results, but tests for hepatitis A and E are not reported. So once again, the cause for the observed abnormalities is not established. The investigator attributed them to “changes in the diet.” Results of tests for hepatitis A and E would be helpful, until which time, dili (mild and transient) cannot be completely excluded. A point against this possibility, however, is that liver tests were improving even before withdrawing the drug.

Conclusion

Based on this group of cases selected for review, no signal for hepatotoxicity is appreciated for canagliflozin at this time.

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/s/

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12/12/2012

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