

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204042Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 15, 2013
From	Jean-Marc Guettier, M.D.C.M
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204042
Supplement#	
Applicant	Janssen Inc.
Date of Submission	May 31, 2012
PDUFA Goal Date	March 31, 2013
Proprietary Name / Established (USAN) names	Invokana (canagliflozin)
Dosage forms / Strength	Immediate release film coated tablet/ 100 and 300 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
Recommended:	Approval

• Introduction

Canagliflozin is a new molecular entity and would introduce to the US market a new class of anti-diabetic agents. Canagliflozin inhibits the sodium glucose co-transporter 2 (i.e., SGLT-2). Inhibition of this glucose co-transporter in the proximal renal tubule decreases urinary glucose reabsorption and promotes urinary glucose excretion. The glucose lowering effect of canagliflozin is thus a result of its glucosuric effect. Glucosuria depends on both prevailing plasma glucose levels and renal function. It is expected that the glucose lowering benefit of canagliflozin will wane with declining renal function. The rise in urinary glucose concentration which results from renal tubular SGLT-2 inhibition by canagliflozin leads to increased urinary water retention and promotes diuresis. SGLT-2 inhibition exerts both a glucose lowering and an osmotic diuretic effect.

A major scientific focus of this memorandum addresses the relationship between the novel mechanism of action and its impact on benefit-risk in segments of the diabetes population with prevalent co-morbid disease (e.g., renal impairment). Another important focus of this memorandum describes the results of the pre-marketing cardiovascular safety evaluation.

• Background

IND 076479 for canagliflozin was opened on May 25, 2007.

In 2008 the FDA issued a Guidance for Industry titled “*Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*”. This Guidance outlined new expectations with regards to pre and post-marketing cardiovascular safety assessment for new products to treat type-2 diabetes.

The applicant’s phase 3 development program was designed after issuance of the guidance with input in the form of face-to-face meetings, teleconferences and written communications from medical and statistical reviewers in the Division of Metabolism and Endocrinology Products. It was agreed that the applicant would use an integrated pre-specified meta-analysis of 9 phase 2 and 3 trials to meet the new expectations related to cardiovascular safety evaluation set forth in the guidance. This plan is described in greater details in the *cardiovascular safety evaluation* section of this memorandum.

• CMC/Device

Chemistry, manufacturing and controls data related to the drug substance manufacturing process were found to be acceptable and are detailed in Dr. Markofsky’s review. The drug substance, canagliflozin, will be manufactured,

packaged and tested by Janssen Pharmaceutical in Geel, Belgium. Testing will also occur by (b) (4). The drug substance is an off-white powder. Janssen has classified the drug substance as a (b) (4).

The presence of a (b) (4) referred from hereon in as (b) (4) in the drug substance was reported to the Agency in an amendment dated 10-23-12 (i.e., several months after original NDA submission). This impurity was also observed to be present in the final drug product. The DEREK Nexus database, for potentially genotoxic impurities, revealed a positive alert for (b) (4) confirmed by positivity on the Ames test. In an amendment dated 11-30-2012, the applicant proposed to update the specification for drug substance release and stability to include limiting the amount of (b) (4). Batch data from samples subject to long term storage (16-31 months) as well as data from samples derived from light and stress stability studies did not indicate accumulation of (b) (4) in the drug substance over time. The (b) (4) limit specification was supported by submitted data and is below the limit of (b) (4) considered acceptable from a pharmacology-toxicology perspective in the final drug product (refer to pages 9-10 in Dr. Alavi's review for full details). The proposed method to quantify the amount of (b) (4) was reviewed and deemed adequate. There were no other impurities in either drug substance or drug product. Stability data supporting a drug substance shelf-life of (b) (4) relative humidity was provided.

Chemistry, manufacturing and control data related to the drug product manufacturing process were found to be acceptable and are detailed in Dr. Sheldon Markofsky's review. The drug product, Canagliflozin, will be manufactured, tested and packaged by Janssen Ortho, LLC in Gurabo, Puerto Rico. Testing will also occur in Titusville, New Jersey and Beerse, Belgium. The drug product is an immediate release, film coated, tablet. Two tablet strengths are proposed: a 100 mg, yellow-colored, capsule-shaped tablet with "100" debossed on one side and "CFZ" debossed on the other and a 300 mg, white colored, capsule-shaped tablet with "300" debossed on one side and "CFZ" on the other. Tablets are (b) (4) containing the drug substance and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, anhydrous lactose, magnesium stearate and microcrystalline cellulose. The film coat (b) (4) contains: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, macrogol/PEG, talc and iron oxide yellow E172 (100 mg tablet only). All inactive ingredients in the blend and film coat are compendial (i.e., United-States Pharmacopeia, National Formulary and/or European Pharmacopeia). The stability studies support an expiration-date of 24 months for all of the proposed commercial container closure systems for both the 100 and 300 mg strengths when stored at controlled room temperature [25°C (77°F)] with excursions permitted between 15°C and 30°C.

Tables detailing container closure systems, tablet counts and national drug code identifier for each of the dose strengths/presentation combinations, reproduced from Dr. Markofsky's review, are shown below.

Figure 1: Packaging 100 mg tablets

Package Type	Count	NDC
(b) (4)	5	50458-140-01
	30	30
	90	90
	500	50
	NA	10

Figure 2: Packaging 300 mg tablets

Package Type	Count	NDC
(b) (4)	5	50458-141-01
	30	30
	90	90
	500	50
	NA	10

CMC has determined that the application qualifies for a categorical exclusion from an environmental assessment.

The biopharmaceutics reviewer, Dr. Houda Mahayni, reviewed the dissolution method and dissolution specifications to be used for registration, batch release and stability testing. Although Dr. Mahayni deemed the proposed dissolution method acceptable; she did not agree with the acceptance criterion proposed (b) (4) because it was not felt to be sufficiently discriminant and suggests that the applicant set the acceptance criterion at Q (b) (4) in 20 minutes. The applicant complied with this request. It was also noted that the commercial product is debossed while the clinical formulation used in pivotal studies was non-debossed. The applicant was asked to submit dissolution profiles comparing the debossed and non-debossed tablets to bridge the two formulations. Comparative data was received and deemed acceptable. The Biopharmaceutics reviewers recommend approval.

The recommendation of the Office of Compliance with regards to the manufacturing facilities inspections is pending at this time.

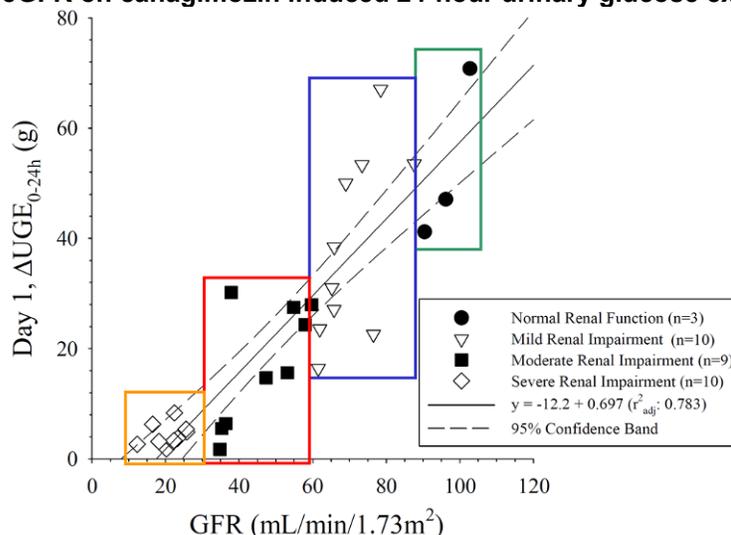
• Nonclinical Pharmacology/Toxicology

The nonclinical reviewers recommend approval of the NDA. Please refer to the reviews by Drs. Fred Alavi, Daniel Minck and Todd Bourcier for a detailed review of the nonclinical pharmacology and toxicology program.

Canagliflozin is a potent, selective, reversible, human sodium glucose cotransporter 2 inhibitor [IC₅₀ value = 4.2 nM]. The sodium glucose cotransporter 2 (SGLT-2) is a low-affinity, high-capacity, active sodium glucose symporter expressed predominantly on the apical membrane of epithelial cells lining the proximal renal tubule. SGLT-2 is responsible for reabsorbing the majority of the filtered glucose load. Inhibition of SGLT-2 by canagliflozin decreases glucose reabsorption and promotes urinary glucose excretion (i.e., promotes glucosuria).

The plasma glucose lowering effect of canagliflozin results from its glucosuric effect. Because glucosuria depends on both prevailing plasma glucose levels and renal function, it is expected that the glucose lowering benefit of canagliflozin will wane with declining renal function. The figure below, taken from DIA1003, illustrates the impact of declining renal function on the pharmacodynamics of canagliflozin (Source: Dr. Hyon Kwon's January 10th 2013 EMDAC presentation). The figure shows that the amount of urinary glucose excreted in the 24 hours following a 200 mg dose of canagliflozin decreases with declining renal function.

Figure 3: Effect of eGFR on canagliflozin induced 24-hour urinary glucose excretion



Canagliflozin was observed to be a much less (160-fold less) potent inhibitor of human SGLT-1 (IC₅₀ = 664 nM). This sodium glucose cotransporter is predominantly expressed on the brush border membrane of enterocytes and plays a key role in intestinal glucose absorption. The applicant states that intestinal drug concentration may reach sufficiently high levels in rats and humans immediately after oral dosing to inhibit SGLT-1 and result in impaired intestinal glucose absorption. This effect is expected to lead to bloating, flatulence and soft stools. Canagliflozin did not inhibit other members of the human sodium glucose cotransporters family (i.e., hSGLT-3, 4 or 6), the human sodium myo-inositol cotransporter (i.e., hSMIT-1) or glucose uptake in cell lines expressing various specific facilitative glucose transporters (i.e., GLUT-1, GLUT-2 and GLUT-4).

Three nonclinical issues of potential relevance to human safety were identified during review of the nonclinical program. The first issue is related to the effect of canagliflozin on bone health observed in general toxicology studies, the second is related to the effect of canagliflozin on the development of renal tubular carcinoma, adrenal pheochromocytoma and Leydig cell tumors observed in the rat carcinogenicity study and the third issue is related to the effect of canagliflozin on body growth and on renal pelvis development observed in a toxicology study conducted in juvenile rats.

Bone and Mineral Metabolism:

In short and long-term rat toxicology studies canagliflozin was observed to cause dose-dependent; trabecular bone accretion (i.e., hyperostosis), soft tissue calcification, increases in urinary calcium excretion (hypercalciuria) and decreases in both circulating levels of hormones involved in calcium homeostasis (i.e., PTH; 25-OH Vitamin D, 1,25 OH Vitamin D, calcitonin) and markers of bone turnover [i.e., serum osteocalcin (bone formation), serum pro-peptide amino terminal of type 1 procollagen (bone formation), urinary deoxypyridinoline (bone resorption)]. These changes occurred at dose levels in the clinical dosing range, were most pronounced in young rats exhibiting rapid skeletal growth and were reversible upon cessation of drug exposure.

The applicant proposes that these changes arise from increased intestinal calcium absorption secondary to SGLT-1 inhibition. Glucose malabsorption caused by inhibition of SGLT-1 is believed to result in intestinal fermentation of malabsorbed sugars and acidification of intestinal luminal content. Acidification of intestinal luminal content in turn increases the solubility and ionization of calcium and augments calcium absorption. The adverse bone effects in rats were shown to be reduced when dietary calcium content was lowered and when fructose, which does not depend on SGLT-1 for absorption, was substituted for other sugars in the rat chow. These two findings were found to be supportive of the applicant's theory.

References establishing that carbohydrate malabsorption can also result in increased calcium absorption in humans are provided in Drs. Bourcier and Alavi's reviews. Because rat toxicology findings were judged relevant to humans the applicant was asked to monitor parameters related to calcium homeostasis and bone health in Phase 3 studies (these findings will be summarized in the safety section of this memorandum). Data derived from a small Phase 1 PK/PD study (DIA1007), however, did not indicate that canagliflozin use was associated with carbohydrate malabsorption in humans. In 14 type 2 DM subjects treated with either canagliflozin 100 mg once daily or 300 mg twice daily for 26 days, no evidence of colonic fermentation (assessed by hydrogen breath test) suggestive of carbohydrate malabsorption was found.

In the chronic rat toxicity (study TOX8574) decreases in bone area (DXA) and bone strength were observed in animals in the mid and high dose group at end-of-study. It is unclear whether these observed changes are attributable to the effect of canagliflozin on mineral metabolism alone, to weight loss associated with canagliflozin use alone or to a combination of these two mechanisms.

Carcinogenicity:

Canagliflozin use was associated with increases in the incidence of renal tubular carcinoma, adrenal pheochromocytoma and Leydig cell tumors in a lifetime-exposure study in Sprague-Dawley rats. No increase in the incidence of specific tumor types was seen in a lifetime-exposure study in CD-1 mice with plasma exposure levels 14-fold above the plasma exposure levels observed for the highest proposed clinical dose. The table below taken from the January 10th EMDAC background package summarizes incident cases of specific tumor types by dose groups for the Sprague-Dawley rat carcinogenicity study.

Table 1: Incidence of Neoplasms in Sprague-Dawley Carcinogenicity Study

(n=65/group)		Canagliflozin, mg/kg			
		0	10	30	100
<i>Multiple of Clinical Exposure</i>			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

Dr. Bourcier in his memorandum notes that the carcinogenicity profile of canagliflozin is consistent with the profiles observed for other members of the SGLT-2 class. Increased incidence of renal tumors, adrenal tumors and/or testicular Leydig cell tumors have been observed in both rats and/or mice for four out of five members of the class reviewed by the division (see Table 2 in the nonclinical background document provided for the January 10th EMDAC meeting).

Canagliflozin was not found to be genotoxic in a standard battery of tests and the clinical pharmacology reviewers conclude that the observed tumors arise through a non-genotoxic mode of action. Nonclinical data in the NDA to support proposed

biological pathways leading to development of specific tumor types in rats are reviewed in Drs. Alavi and Bourcier's memoranda.

Leydig cell tumors in rats are believed to develop as a consequence of an observed rise in luteinizing hormone (LH) plasma levels and a heightened sensitivity of rat Leydig cells to the trophic action of the hormone (i.e., due increased LH receptor density compared to humans). The nonclinical reviewers conclude that the risk to humans is minimal since canagliflozin was not observed to cause a rise in LH levels in humans and LH receptor density on human Leydig cells is lower than that of rat.

Carbohydrate malabsorption and calcium imbalance are invoked as key proximal events required for the development of both renal and adrenal tumors in rats. Drs. Alavi and Bourcier have reviewed literature and nonclinical data submitted to the NDA supporting a role for these two events in tumorigenesis and agree with the applicant's conclusion that these events are necessary for renal and adrenal tumor development. The non-clinical reviewers are reassured by the fact that the large changes related to carbohydrate absorption and calcium metabolism seen in rats were not seen in clinical studies and by the fact that exposure at the highest proposed clinical dose is 5 to 7 fold lower than the lowest exposure which caused tumors in animals. In light of these findings, Dr. Bourcier assesses the risk to humans as being low. Furthermore he recommends that the incidence of these tumors be monitored in the post-market setting because: the distal events in tumorigenesis are at present unknown; the proximal renal tubule is a direct target of canagliflozin; and canagliflozin would represent the first marketed therapeutic in the SGLT-2 class.

Reproductive Toxicology

Canagliflozin caused renal pelvis and renal tubule dilatation as well as a decrease in the rate of body growth in juvenile rats. Post-natal week 3 to 6 was identified as the time window of susceptibility for the toxic renal effect. This window covers the period of morphological and functional kidney development in rats and would correspond to the second/third trimesters of pregnancy in humans. Furthermore canagliflozin was found to be present in the milk of lactating rats and is transferred in sufficient quantity to weaning pups to affect body weight. Drs. Minck and Bourcier agree that canagliflozin presents a developmental risk to the fetus and to the newborn if exposed during nursing. The findings support a pregnancy category C and recommendations to discontinue use of canagliflozin during the second and third trimester of pregnancy and during nursing in the Highlight and Warning and Precautions sections of the label.

• **Clinical Pharmacology/Biopharmaceutics**

The clinical pharmacology reviewers recommend approval of the NDA. Please refer to the review co-authored by Drs. Jayabharathi Vaidyanathan, Manoj Khurana, Suryanarayana Sista, Lokesh Jain, Anshu Marathe, Nitin Mehrotra, Lyle Canida, and Michael Pacanowski for details.

At the time of NDA submission 40 phase 1 trials had been conducted with canagliflozin. These included single and multi-dose pharmacokinetic (PK)/ pharmacodynamics (PD) studies, studies evaluating the effect of age, race, sex, renal and hepatic function on PK characteristics, drug-drug interactions studies, mechanistic studies and specific clinical pharmacology safety studies to evaluate canagliflozin's arrhythmogenic and phototoxic potential.

The absolute bioavailability of canagliflozin after an oral dose was found to be 65%. The median time to reach maximal plasma concentration (T_{max}) was observed to range from 1 to 2 hours. Maximum and total drug exposure was dose proportional in the 50 to 300 mg dose range. Food had no effect on pharmacokinetic (PK) parameters. Steady state concentration was reached after 4 to 5 days of once daily dosing. Accumulation at steady state based on area under the drug concentration curve after multiple doses was minimal (accumulation ratio range: 1.29-1.36).

In plasma, canagliflozin is extensively protein bound (i.e., 98.3-99.2%) predominantly to albumin. Canagliflozin has widespread tissue distribution (V_{ss} 119 liters). The blood to plasma ratio ranging from 0.66-0.71 suggests canagliflozin preferentially distributes to plasma rather than the cellular elements of blood.

Canagliflozin circulates mostly unchanged in plasma. The main metabolic pathway in humans is through hepatic O-glucuronidation. Uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) forms one of the major O-glucuronide metabolite (M7) and UGT2B4 the other major O-glucuronide metabolite (M5). Neither metabolite was shown to be active *in vitro*. Metabolism of canagliflozin by the cytochrome P450 system is minimal.

The apparent terminal half-life is 10.6 hours for the 100 mg dose and 12.1 hours for the 300 mg dose. The major elimination pathway (i.e., 60%) is through biliary excretion. 32.5% is eliminated in the urine mostly in the form of metabolites (i.e., <1% unchanged canagliflozin was recovered).

No dose adjustment based on age, race or gender is recommended. No dose adjustment is recommended for subjects with mild or moderately impaired renal function down to an eGFR of 40 mL/min/1.73 m². Use of canagliflozin is not recommended in patients with an eGFR of 40 mL/min/1.73 m² or less due to lack of glycemic efficacy and augmented risk attributable to the diuretic effect of canagliflozin. No dose adjustment is recommended for subjects with Child-Pugh mild or moderate liver impairment. The sponsor states that use of canagliflozin is not recommended in patients with severe liver impairment because this population has not been evaluated. The clinical pharmacology team believes the available data support use of canagliflozin in patients with severe impairment provided adequate caution is used.

Results of *in vitro* studies have shown that canagliflozin has moderate inhibitory activity for some of the cytochrome P450 enzymes (i.e., CYP2B6 and CYP3A4) but

does not induce cytochrome P450. The sponsor conducted drug-drug interaction (DDI) studies with the following CYP2C9 and CYP3A4 enzyme substrates: simvastatin, glyburide, the oral contraceptives ethinyl estradiol and levonorgestrel and warfarin. The clinical pharmacology reviewer has determined these drug interactions to not be clinically relevant and is not recommending dosage adjustment in these settings.

Results from vitro studies have shown that canagliflozin is both a substrate for p-glycoprotein and a weak p-glycoprotein inhibitor. The applicant has conducted a DDI study with cyclosporine (P-glycoprotein inhibitor) to evaluate the impact P-glycoprotein inhibition on canagliflozin PK. The clinical pharmacology reviewer has determined that no dosage adjustment in this setting is necessary. The applicant also conducted a DDI interaction study to evaluate the impact of canagliflozin induced p-glycoprotein inhibition on digoxin PK. The clinical pharmacology reviewer has determined that the recommendation to monitor digoxin level when it is co-administered with canagliflozin is acceptable.

Canagliflozin is metabolized by uridine diphosphate glucuronosyltransferase (UGT) enzymes. The applicant carried out a DDI study to evaluate the effect of UGT inhibition by probenecid on canagliflozin PK. Changes to canagliflozin PK in the setting of probenecid co-administration were not clinically relevant. The applicant carried out a DDI study to evaluate to effect of UGT induction by rifampin on canagliflozin PK. Rifampin was shown to lower total and maximal canagliflozin exposure. The clinical pharmacology reviewer recommends using the higher dose of canagliflozin if it is to be co-administered with rifampin and to monitor HbA1c for loss of efficacy in this setting.

Finally, the applicant carried out interaction studies to evaluate the effect of canagliflozin on acetaminophen, metformin and hydrochlorothiazide PK respectively. No dose adjustment is recommended when canagliflozin is used with these products.

Dr. Zhang from the Interdisciplinary Review Team (IRT) for QT studies has reviewed the results of the sponsor's Thorough QT (TQT) study and has concluded that canagliflozin does not prolong the QT interval. The upper bound of the 2-sided 90% confidence interval around the time-averaged baseline-adjusted mean differences in QTcF between canagliflozin and placebo was 2.9 and 2.2 msec for the 300 mg and 1200 mg dose, respectively. A positive response was elicited from moxifloxacin establishing assay sensitivity. For both canagliflozin doses the upper bound is below the 10 msec threshold for concern described in the ICH E14 guideline and indicates no clinically relevant effect of canagliflozin on QT/QTc. Furthermore no relationship between change in QTcF from baseline and canagliflozin concentration was seen. Maximum drug concentration achieved with the 1200 mg dose was 2.6 times that of the highest to-be-marketed dose (i.e., 300 mg). Key pharmacology studies evaluating the effect of a multi-dose regimen, intrinsic and extrinsic factors on maximum exposure support the adequacy of the suprathreshold dose used in the TQT study.

During development the applicant added (b) (4) to the drug substance manufacturing process so as (b) (4) of the active pharmaceutical ingredient (i.e., API). Drug substance manufactured in this manner is referred to as (b) (4) will be used to manufacture the commercial drug product. (b) (4) was used to manufacture drug product for some of the pivotal trials. Clinical pharmacology has reviewed comparative particle size distribution data for Phase 2 and 3 drug product manufactured using (b) (4) lots. Particle size distribution was found to be similar between drug products relying on (b) (4). In addition, population PK analysis did not reveal PK differences between drug products manufactured using (b) (4). Clinical pharmacology therefore concludes that drug product manufactured using (b) (4) is similar to drug product manufactured using (b) (4).

Over-encapsulation was used for blinding purposes in all Phase 3 trials. Dr. Vadayanathan reviewed comparative bioavailability data between over-encapsulated and non-over-encapsulated canagliflozin and has concluded that the effects of over-encapsulation on bioavailability were not clinically relevant.

Finally, drug product used for the Phase 2b trials were manufactured using a (b) (4) while drug product used for the Phase 3 trials and commercial products are manufactured using a (b) (4). The applicant conducted a bioequivalence study (DIA1017) to compare the relative bioavailability of drug products manufactured using these two processes. The two products were found to be bioequivalent.

- **Clinical/Statistical- Efficacy**

This section will focus on the main efficacy results derived from the nine controlled Phase 3 clinical trials in NDA 204042. Please refer to Dr. Liu's and Hyon's reviews for details.

Efficacy and safety data from nine Phase 3 trials were included in the NDA. All Phase 3 trials were randomized, double-blind, multicenter, multi-national placebo or active controlled trials. Two doses of canagliflozin were studied in each of the nine Phase 3 trials (i.e., 100 mg and 300 mg) and randomization to canagliflozin 100, canagliflozin 300 and comparator was 1:1:1 across all trials. Six trials evaluated canagliflozin in a general diabetes population and three trials enrolled specific subpopulations of patients with diabetes. Finally, three substudies in two of these trials were carried out.

Six trials were designed to establish the glucose-lowering effect of canagliflozin in a general population of adults with type 2 diabetes (i.e., age \geq 18 years; HbA1c $>$ 7.0%). The primary efficacy endpoint in these trials was assessed at either 26 or 52 weeks. Five out these six trials had non-voluntary active/placebo controlled extensions.

The glucose lowering effect of canagliflozin in the general diabetes population was evaluated in the following clinical settings:

Monotherapy

- **DIA3005 - 26-week trial**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - This trial had a double blind 26-week active controlled (sitagliptin 100 mg) extension

Add-on to Metformin

- **DIA3006 - 26 week trial**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - This trial had a double blind 26-week active controlled (sitagliptin 100 mg) extension
- **DIA3009 - 52 week trial**
 - Compared canagliflozin (100 and 300 mg) to maximum tolerated glimepiride dose (i.e., up to 6-8 mg according to country specific label)
 - This trial had a double blind 26-week extension

Add-on to Metformin and another anti-diabetic agent

- **DIA3002: add on to metformin and sulfonylurea - 26 week trial**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - This trial had a double blind 26-week placebo controlled extension
- **DIA3012: add on to metformin and pioglitazone - 26 week trial**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - This trial had a double blind 26-week controlled extension (sitagliptin 100 mg)
- **DIA3015: add on to metformin and sulfonylurea - 52 week trial**
 - Compared canagliflozin (100 and 300 mg) to sitagliptin (100 mg)

Two trials were designed to establish the glucose lowering effect and the safety of canagliflozin in special populations.

Renal Impaired (stable eGFR ranging from 30 to less than 50 mL/min/1.73 m²)

- **DIA3004: monotherapy or add-on to stable anti-diabetic - 26 week trial**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - This trial had a double blind 26-week placebo controlled extension

Older Adults (males and post-menopausal females between 55 to 80 years)

- **DIA3010: monotherapy or add-on to stable anti-diabetic-26 week trial**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - This trial had a double blind 78-week placebo controlled extension

One trial was designed to establish the cardiovascular safety of canagliflozin in a population of type 2 diabetes patients with established or at high risk of cardiovascular disease. A brief trial description and results of the interim cardiovascular safety analysis will be discussed in the safety section of this memorandum.

Cardiovascular Safety

- **DIA3008: cardiovascular outcomes trial - time to event trial**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - Used as monotherapy or as add-on to any antidiabetic regimen
 - This trial is ongoing

Three substudies within two trials were also carried out.

- **DIA3008 add-on to sulfonylurea substudy – 18 weeks**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - Sulfonylurea used at protocol specified doses (see below)
 - Sulfonylurea used either alone or in combination with other anti-diabetic agents
- **DIA3008 add-on to insulin substudy – 18 weeks**
 - Compared canagliflozin (100 and 300 mg) to placebo
 - Baseline insulin dose at least ≥ 20 IU day
 - Insulin used either alone or in combination with other anti-diabetic agents
- **DIA3005 monotherapy high glycemic cohort substudy - 26 weeks**
 - Baseline HbA1c $>10\%$
 - Canagliflozin 100 and 300 mg uncontrolled

A pre-treatment phase of up to 12 weeks was built in to the design of all trials. Subjects not on protocol-specified background therapy at screening entered a ≥ 10 week washout/dose optimization pre-treatment period. Maximally effective doses of background therapy were required in all trials. For add-on to metformin trials the required dose was ≥ 2000 mg/day or ≥ 1500 mg if not tolerated. A $\frac{1}{2}$ maximum dose of sulfonylurea was required in add-on to sulfonylurea trials. For the trial using background pioglitazone a dose of ≥ 30 mg/day was required.

Eligible subjects on stable, protocol-specified, background therapy entered a 2-week placebo run-in period. Randomization of eligible subjects followed the run-in period and was stratified in all trials. Stratification variables differed across the nine trials

and were related to the type of pre-trial anti-diabetic medications used, the country of participation, the baseline glycemic control level, the baseline bone mineral density T score or the presence of baseline cardiovascular disease (Refer to Table 4 in Dr. Kwon's review).

The phase 3 glycemic efficacy trials and substudies had similar inclusion criteria.

Key entry criteria included age between 18-80 years for all trials except trials DIA3004, DIA3008 and DIA3010. In these three trials, subjects were required to be > 25, 30 and 55 years old at screening, respectively. All enrolled subjects were to have inadequately controlled type 2 diabetes defined by specific HbA1c ranges at screening. The HbA1c range varied appropriately across and within trials according to type of pre-trial anti-diabetic medication, disease stage and trial design (e.g., 6.5-9.5%, 7-10%, 7-11%, 7.5-10% or 10-12%). Women of childbearing potential were allowed to participate if they were surgically sterile or practicing adequate contraception. In the trial evaluating the effect of canagliflozin on bone mineral density (i.e., DIA3010) women were required to have been post-menopausal for at least three years prior to screening. In DIA3004 only subjects who had a stable 4-variable MDRD eGFR (i.e., <25% decline between screening and start of run-in taken 4-weeks apart) ranging from 30 to less than 50 mL/min/1.73 m² were eligible to participate.

Similar exclusion criteria were used across the Phase 3 program. The following subjects were ineligible to participate.

- Subjects with severe hypoglycemic episode in the last six months
- Subjects with active hepatitis, liver disease or abnormal liver laboratory tests [i.e., alanine aminotransferase (i.e., ALT) > 2.0 the upper limit of normal or total bilirubin > 1.5 times the ULN]
- Subjects on hemodialysis or with nephrotic range proteinuria or with inflammatory renal disease
- Subjects with an eGFR below 55 mL/min/1.73 m² in all add-on to metformin trials (note: in some countries; country specific metformin label eGFR or creatinine based criteria were used).
- Subjects with an eGFR below 50 mL/min/1.73 m² in the monotherapy trial (DIA3005) and older adult trial (DIA3010).
- Subjects with an eGFR below 30 mL/min/1.73 in DIA3008 (male and female subjects using metformin at baseline were ineligible if their creatinine was ≥ 1.4 and 1.3 mg/dL respectively).
- Subjects with unstable angina, myocardial infarction, stroke or who underwent a revascularization procedure in the three months preceding screening
- Subjects with NYHA Class 3 and 4 heart failure (except in DIA3008 where only NYHA Class 4 heart failure was excluded)
- Subjects with uncontrolled hypertension

The primary efficacy endpoint for all Phase 3 trials was the change in hemoglobin A1c (i.e., HbA1c) from baseline to Week 26 except for trials DIA3009, DIA3015 and the

two sub-studies in DIA3008. In trial DIA3009 and DIA3015, a change from baseline to Week 52 was used. In the two sub-studies a change from baseline to Week 18 was used.

Other secondary endpoints considered included: the change in fasting plasma glucose from baseline to end of study; the change in 2-hour post-meal glucose (2-hr PPG) from baseline to end of study; the proportion of subjects achieving target glycemic control (i.e., HbA1c < 7%) at end of study; the percent change in body weight from baseline to end of study; the percent change in HDL-C from baseline to end of study; the percent change in triglycerides to end of study; and the percent change in systolic blood pressure from baseline to end of study. To control family wise Type-1 error when multiple hypotheses were tested, the applicant relied on a sequential testing procedure based on a pre-specified testing hierarchy. When more than one family of hypotheses was tested in a trial the applicant modified the alpha-level using a Hochberg procedure. The exact hierarchical order and alpha-adjustment methods used differed slightly across trials and are detailed in Dr. Liu's review.

The primary statistical population used for each trial was the modified intent-to-treat population (mITT) population which consisted of all randomized patients exposed to at least one dose of canagliflozin. Dr. Liu also performed supportive analyses on the per protocol population which consisted of the mITT subjects who completed the study to end of treatment, were not rescued and had no protocol violations.

For each trial, the between group difference in HbA1c change from baseline to end of trial (LS mean treatment difference) and its associated two-sided 95% confidence interval was estimated from an ANCOVA model which included terms for treatment and randomization strata (if appropriate) as fixed effects and baseline HbA1c as covariate. In specific studies other terms were included in the analysis model (refer to Dr. Liu's review for details). Missing data were handled using a last observation (LOCF) carried forward strategy. Dr. Liu performed supportive analyses using mixed-model repeated measures (MMRM) and found results consistent with the applicant's model. A pre-specified, appropriate, non-inferiority margin of 0.3% was used in the trials comparing canagliflozin to the active comparators glimepiride (3009) and sitagliptin (3015).

Baseline Characteristics:

Drs. Kwon and Liu discuss patient baseline characteristics in details.

Demographic, anthropometric and disease characteristics were similar across the six trials carried out in a general diabetes population (refer to Tables 7, 8, and 9 in Dr. Kwon's review). The mean age of participants in these trials ranged from 55-57 years. Most subjects were White (~70%) or Asians (~15%). Blacks accounted for 3.5 to 12% of participants depending on the trial. Hispanics represented 9 to 31% of all participants. Participants were on average obese per BMI criteria (i.e., BMI \geq 30 kg/m²), had an estimated glomerular filtration rate (eGFR) in the normal range (i.e., \geq

80 mL/min/1.73 m²) and had on average good blood pressure control (mean SBP ≤ 130 mm Hg). Subjects had had diabetes for an average of 4, 7 and 10 years in the monotherapy, add-on to metformin and add-on to two anti-diabetic agents trials, respectively, at the time of enrollment and 6 to 33% had known microvascular complications of their disease (HbA1c at baseline is shown in the table below).

Subjects were older in trials carried out in special patient populations. The mean age was 69, 65 and 64 years in DIA3004, DIA3008 substudies and DIA3010, respectively. Subjects in these trials also had worse renal function based on eGFR (mean baseline eGFR ~ 40, 70 and 80 mL/min/1.73 m² in DIA3004, DIA3008 substudies, DIA3010, respectively) and blood pressure control at baseline (mean SBP ≥ 130 mm Hg). Patients enrolled in these studies had the longest duration of diabetes (i.e., 10-17 years) and were more likely to have microvascular complications from their disease (i.e., 30 to 80%).

Primary Efficacy Results:

The main efficacy results shown in the table below are taken from Dr. Liu's review. The table summarizes the estimated mean change in HbA1c from baseline in the mITT population using LOCF as well as the between group difference and 95% CI for each of the key comparisons in the nine pivotal trials.

Table 2: Change in HbA1c (%) from baseline to end-of-treatment (mITT population LOCF)

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

After 26 weeks of treatment the 100 and 300 mg doses of canagliflozin provided superior glucose lowering compared to placebo in the monotherapy setting (DIA3005), when added to a maximally effective background dose of metformin (DIA3006) and when added to either a background regimen including maximally effective doses of metformin and sulfonyleurea (DIA3002) or metformin and pioglitazone (DIA3012). Findings in older adults and in the two 18-week substudies evaluating co-administration of canagliflozin with insulin or sulfonyleurea in T2DM patients at risk or with established CV disease were consistent with the overall

findings. Sensitivity analyses based on MMRM rather than LOCF or the per protocol population were also consistent with the overall findings (See Dr. Liu's review for details).

Glucose lowering achieved after 52 weeks of treatment with either the 100 and 300 mg doses of canagliflozin was non-inferior to the glucose lowering achieved using either a maximally effective dose of glimepiride (DIA3009) or sitagliptin (DIA3015) (i.e., upper bound of the 95% CI below the pre-specified non-inferiority margin of 0.3%). The amount of glucose lowering achieved with canagliflozin 300 mg was statistically greater than that achieved using glimepiride or sitagliptin at the end of 52 weeks. The effect size difference between canagliflozin 300 mg and glimepiride was small (i.e., 0.12%) but larger between canagliflozin 300 mg and sitagliptin (0.37%).

Tripling the canagliflozin dose reduced baseline HbA1c by an additional 0.1 to 0.25%. This observation is consistent with a modest dose response.

Appendix figures 1.3 to 10.3 in Dr. Liu's review graph the changes in HbA1c from baseline observed over several timepoints for each of the Phase 3 studies and substudies. These figures show that the most rapid rate of glucose lowering occurs early, that the maximum glucose lowering effect is observed between 12 and 26 weeks depending on the trial and that a significant difference from baseline persists until the last time point checked (i.e., greatest duration 52 weeks). These data support the notion that canagliflozin offers durable glycemic control in the population of individuals studied. Although the rate of glucose lowering differs between canagliflozin and the two active comparators (glimepiride DIA3009 and sitagliptin DIA3015) the graphs do not suggest canagliflozin offers an appreciable benefit in terms of durability over comparators.

Special Population Study: Moderate Renal Impaired (eGFR < 60 mL/min/1.73 m²)

Study DIA3004

The applicant was asked to quantify, by means of a dedicated clinical trial, the glucose-lowering effect of canagliflozin in a population of patients with moderate renal impairment because primary pharmacology predicts a lower glycemic benefit in this population and because the prevalence of chronic kidney disease (CKD) in diabetes is high. According to the 2005-2010 National Health and Nutrition Survey approximately ~20% (19.6 %) of patients with diabetes had chronic kidney disease defined by an estimated GFR below 60 mL/min. (Source: United States Renal Data System; 2012 Atlas of CKD and ESRD).

In trial DIA3004 (i.e., mean eGFR 39 mL/min/1.73m²), the magnitude of glucose lowering achieved by canagliflozin was observed to be reduced by approximately 50%, for each respective dose (refer to Table 2 above). A dose response in this subpopulation of patients was still observed. The lower margin of the estimate comparing the treatment effect of canagliflozin 100 mg to placebo approached zero.

Subgroup Analyses: Pooled Moderate Renal Impaired Population

The applicant pooled patients with moderate renal impairment across trials DIA3004, DIA3005, DIA3008 and DIA3010 to further analyze the relationship between renal function defined by eGFR and glucose lowering effect of canagliflozin. The results of this pooled analysis were consistent with the observation made in the dedicated renal impairment trial (DIA3004). Results show that efficacy of canagliflozin declines with worsening renal function. Subjects with baseline eGFR below 45 mL/min/1.73 m² randomized to canagliflozin 100 mg per day had very modest reduction in HbA1c from baseline and this difference was close to being non-significant compared to placebo. The results for the mITT population (LOCF) arranged by baseline eGFR categories are shown below (Adapted from Table 3.2.5.1 in Dr. Liu's review).

Table 3: Effect of eGFR < 60 mL/min/1.73 m² on HbA1c lowering (Pool of Trials DIA3004, DIA3005, 3008 and 3010)

	Treatment Arm	n	Baseline Mean ± SE	LS Mean Change ± SE	LS mean difference (95% CI)
eGFR ≥ 30 but less than 60 mL/min/1.73 m²					
	Cana 300 mg	354	8.07 ± 0.05	-0.62 ± 0.06	-0.47 (-0.60, -0.35)
	Cana 100 mg	326	8.09 ± 0.05	-0.52 ± 0.06	-0.38 (-0.50, -0.26)
	Placebo	356	7.98 ± 0.07	-0.14 ± 0.06	
eGFR ≥ 30 but less than 45 mL/min/1.73 m²					
	Cana 300 mg	122	8.10 ± 0.08	-0.34 ± 0.19	-0.39 (-0.61, -0.17)
	Cana 100 mg	118	8.08 ± 0.09	-0.18 ± 0.19	-0.23 (-0.45, -0.01)
	Placebo	108	8.10 ± 0.09	+0.05 ± 0.19	
Subgroup: eGFR ≥ 45 but less than 60 mL/min/1.73 m²					
	Cana 300 mg	232	8.10 ± 0.06	-0.62 ± 0.07	-0.52 (-0.66, -0.38)
	Cana 100 mg	208	8.11 ± 0.06	-0.57 ± 0.07	-0.47 (-0.61, -0.32)
	Placebo	248	7.98 ± 0.06	-0.10 ± 0.07	

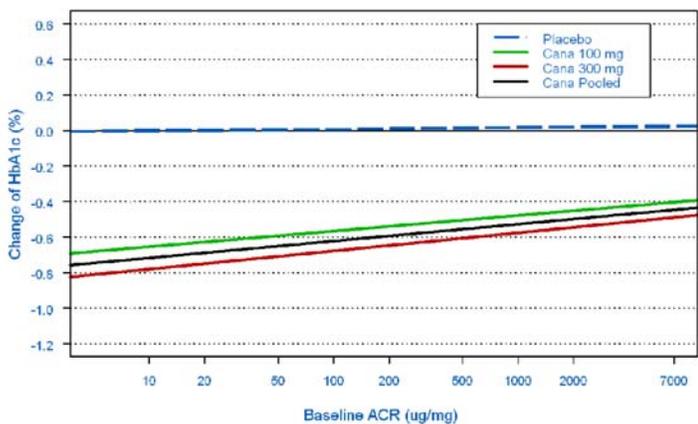
Proteinuria

Proteinuria is another marker of renal dysfunction prevalent in the diabetes population. Canagliflozin is highly protein bound and its site of action lies on the apical membrane (i.e., tubular side) of proximal tubular cells. To evaluate how the presence of tubular protein impacts drug response, the applicant was asked to characterize the influence of baseline degree of proteinuria, independent of eGFR, on the glucose lowering effect of canagliflozin.

The applicant performed post-hoc pooled analyses of trials where a measure of proteinuria had been obtained at baseline [i.e., albumin to creatinine ratio (ACR)]. In these analyses the ANCOVA model generally included terms for treatment, study and covariates for baseline HbA1c, baseline eGFR, baseline Log₁₀ ACR and the

interaction term baseline $\text{Log}_{10} \text{ACR} \times \text{treatment}$ (refer to eCTD sequence #18: 12/19/2012 for specific models). Significant interactions between baseline ACR and treatment were found in these analyses. Graphical representation of the model obtained by pooling placebo controlled trials DIA3004, DIA3005 and DIA3008 suggests decreasing canagliflozin response with increasing proteinuria at baseline, independent of eGFR. In this model the interaction p-value comparing pooled canagliflozin to placebo was 0.0026.

Figure 4: Model Fit of baseline ACR on HbA1c Change from Baseline PBO-control pool (Source: eCTD sequence #18: 12/19/2012)

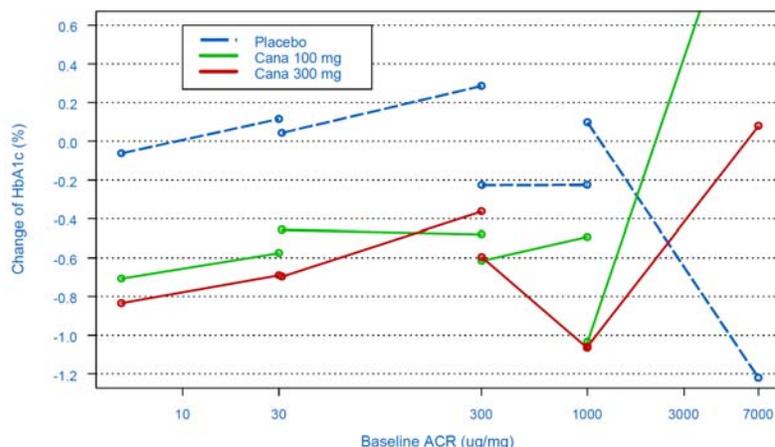


After reviewing scatter-plots depicting the relationship between baseline ACR and HbA1c response, the applicant explored the effect of proteinuria according to four clinically relevant baseline proteinuria subgroups (i.e., $\text{ACR} < 30 \mu\text{g}/\text{mg}$, $30 \leq \text{ACR} \leq 300 \mu\text{g}/\text{mg}$, $300 \leq \text{ACR} \leq 1000 \mu\text{g}/\text{mg}$ and $> 1000 \mu\text{g}/\text{mg}$). This additional analysis demonstrated that the most significant interaction occurred in the subgroup of individuals with baseline proteinuria $\geq 1000 \mu\text{g}/\text{mg}$ (see figure below). This subgroup also constituted the smallest number of individuals (~2%) limiting reliability of conclusions from this subgroup (see table below). It also raises questions concerning the validity of the estimate obtained in figure 3 (i.e., slope of the fitted line could be influenced by a few extreme outliers).

Table 4: Number and Proportion of Individuals by ACR subgroups

< 30 $\mu\text{cg}/\text{mg}$	30 to < 300 $\mu\text{cg}/\text{mg}$	300 to < 1000 $\mu\text{cg}/\text{mg}$	> 1000 $\mu\text{cg}/\text{mg}$
n=3538	n=1051	n=200	n=103
72%	21%	4%	2%

Figure 5: Model Fit of baseline ACR by subgroups on HbA1c Change from Baseline PBO control pool (Source: eCTD sequence #18: 12/19/2012)



Reviewer Comment: These and additional exploratory analyses provided by the applicant do not suggest a large independent effect of proteinuria on drug response in the microalbuminuria range (< 300 $\mu\text{g}/\text{mg}$). Proteinuria in the macroalbuminuria range may impact the response to canagliflozin but too few individuals with this level of proteinuria at baseline participated in Phase 3 trials to reliably assess this possibility.

Other Subgroup Analyses:

The impact of age, gender, race, ethnicity, geographical region and baseline BMI on the placebo adjusted change in HbA1c from baseline to end of trial was explored by the applicant using a dataset which pooled participants from the following placebo controlled trials: DIA3005, DIA3006, DIA3008 (sulfonylurea and insulin substudies), DIA3002 and DIA3012. The result of this analysis is shown in Figure 12 of Dr. Kwon's review. Dr. Liu also explored the influence of these baseline characteristics on efficacy across each individual study (see forest plots in Appendix figures 11.1-11.9 in his review). No significant interactions to suggest glycemic response differed across any category of the above-listed baseline characteristics were found except in Study 3006 where subjects who were ≥ 65 years old at baseline had a smaller treatment effect than younger subjects.

Dr. Liu performed an additional analysis (refer to Table 3.2.5.3 in his review) exploring the effect of age categories on drug response by adding trial DIA3004 (trial with the eldest individuals at baseline) and DIA3010 (older adult trial) to the pool of placebo control trials listed above. When these studies are added to the placebo-controlled pooled analysis, the interaction between age and response becomes significant (p -value < 0.01) and suggests that response decreases with advancing age. However, even in the eldest age category considered (≥ 75 years at baseline) the effect size difference between treatment and placebo remained both clinically and statistically significant (mean canagliflozin to placebo difference in mITT LOCF population $\sim -0.5\%$).

In both the applicant's and Dr. Liu's analyses significant interactions suggesting efficacy response differs across baseline HbA1c (i.e., higher HbA1c greater response) and eGFR categories (this was discussed above and is expected based on the drug's pharmacology) were found. The HbA1c interaction is a common observation across classes of antidiabetics.

Secondary Endpoints

Glycemic: Fasting Plasma Glucose, 2-hr PPG and Responder Analyses

Results of analyses for secondary glycemic endpoints were consistent with findings based on reduction in HbA1c from baseline. The findings support a conclusion that canagliflozin resulted in clinically and statistically significant reductions in both fasting and post prandial glucose (DIA3005 and DIA3006 only) in multiple use settings. The findings are also consistent with a modest dose response.

A greater proportion of individuals (~10-20% more) achieved the recommended American Diabetes Association glycemic target of an HbA1c < 7% at end of trial on the 300 mg compared to the 100 mg dose. The difference in the proportion of responders between the 100 mg and placebo dose, although numerically different, was not statistically significant in subjects with a mean baseline eGFR of 39 mL/min/1.73m² (DIA3004).

Dr. Liu was able to replicate the applicant's analyses in the mITT population using LOCF and shows these results for each secondary glycemic endpoint by individual studies across multiple tables in his review. He also performed a responder analysis excluding all subjects who had an HbA1c of < 7% at baseline. Results using this strategy were qualitatively similar to the applicant's analysis which examined the proportion of individuals who ended the trial with an HbA1c below 7% regardless of baseline HbA1c value. From a labeling standpoint, I agree that Dr. Liu's analysis represents a more orthodox responder type analysis. The tables below are replicated from tables 14 and 16 in Dr. Kwon's review.

Table 5: Change in FPG (mg/dL) from baseline to end-of-trial (mITT population LOCF)

Study (Weeks)	Treatment Arm	n	Baseline Mean (SD)	LS Mean Change ± SE	LS mean difference (95% CI)	p-value
Monotherapy						
DIA3005 (26) Main study	Cana 300 mg	192	173 (43)	-35 ± 2	-43 (-50, -37)	<0.001
	Cana 100 mg	188	172 (43)	-27 ± 2	-36 (-42, -29)	<0.001
	Placebo	184	166 (39)	8 ± 2		
Add-on to background metformin						
DIA3006 (26) Add-on to metformin	Cana 300 mg	360	173 (45)	-38 ± 2	-40 (-46, -34)	<0.001
	Cana 100 mg	365	169 (41)	-27 ± 2	-30 (-36, -24)	<0.001
	Placebo	181	164 (38)	2 ± 3		
DIA3009 (52) Add-on to metformin	Cana 300 mg	476	164 (36)	-27 ± 2	-9 (-13, -5)	
	Cana 100 mg	477	165 (37)	-24 ± 2	-6 (-10, -2)	
	Glimepiride	477	166 (38)	-18 ± 2		
Add-on to dual combination therapy						
DIA3002 (26) Add on to metformin+SU	Cana 300 mg	152	168 (38)	-31 ± 4	-35 (-44, -25)	<0.001
	Cana 100 mg	155	173 (41)	-18 ± 4	-22 (-31, -13)	<0.001
	Placebo	150	170 (39)	4 ± 4		
DIA3012 (26) Add on to metformin+PIO	Cana 300 mg	112	164 (41)	-33 ± 3	-36 (-43, -28)	<0.001
	Cana 100 mg	113	169 (39)	-27 ± 3	-29 (-37, -22)	<0.001
	Placebo	114	164 (40)	3 ± 3		
DIA3015 (52) Add on to metformin+SU	Cana 300 mg	365	170 (48)	-30 ± 3	-24 (-30, -18)	<0.001
	Sitagliptin	374	164 (44)	-6 ± 2		
Special Population						
DIA3010 (26) Older Adults	Cana 300 mg	229	153 (37)	-20 ± 3	-28 (-34, -21)	<0.001
	Cana 100 mg	239	161 (39)	-18 ± 3	-26 (-32, -19)	<0.001
	Placebo	232	156 (39)	7 ± 3		
DIA3004 (26) Moderate Renal Impairment	Cana 300 mg	89	159 (58)	-12 ± 5	-12 (-25, 1)	0.07
	Cana 100 mg	88	169 (46)	-15 ± 5	-15 (-28, -2)	0.02*
	Placebo	87	161 (44)	0.5 ± 5		
DIA3008 (18) SU substudy	Cana 300 mg	39	177 (37)	-36 ± 6	-48 (-64, -31)	<0.001
	Cana 100 mg	40	185 (45)	-25 ± 6	-38 (-53, -20)	<0.001
	Placebo	40	185 (48)	-12 ± 6		
DIA3008 (18) Insulin substudy	Cana 300 mg	572	168 (52)	-25 ± 2	-29 (-34, -24)	<0.001
	Cana 100 mg	551	170 (47)	-19 ± 2	-23 (-28, -17)	<0.001
	Placebo	545	169 (49)	4 ± 2		

Table 6: Proportion of Subjects with an HbA1c < 7 % at end-of-trial (mITT population LOCF)

Study (Weeks)	Treatment Arm	n	% achieving target	%Diff (minus comparator)	95% CI	p-value
Monotherapy						
DIA3005 (26) Main study	Cana 300 mg	193	62.4	41.7	32.3;51.2	<0.001
	Cana 100 mg	191	44.5	23.9	14.2;33.5	<0.001
	Placebo	189	20.6			
Add-on to background metformin						
DIA3006 (26) Add-on to metformin	Cana 300 mg	360	57.8	27.9	19.2;36.8	<0.001
	Cana 100 mg	365	45.5	15.6	24.5;6.8	<0.001
	Placebo	181	29.8			
DIA3009 (52) Add-on to metformin	Cana 300 mg	474	60.1	4.3	-2.2;10.8	
	Cana 100 mg	478	53.6	-2.3	-8.8;4.3	
	Glimepiride	473	55.8			
Add-on to dual combination therapy						
DIA3002 (26) Add on to metformin+SU	Cana 300 mg	152	56.6	38.6	27.9;49.2	<0.001
	Cana 100 mg	155	43.2	25.2	14.6;35.8	<0.001
	Placebo	150	18.0			
DIA3012 (26) Add on to metformin+PIO	Cana 300 mg	112	64.3	31.8	18.6;45.1	<0.001
	Cana 100 mg	113	46.9	14.4	1.0;27.9	0.007
	Placebo	114	32.5			
DIA3015 (52) Add on to metformin+SU	Cana 300 mg	365	47.6	12.3	4.9;19.6	
	Sitagliptin	374	35.3			
Special Population						
DIA3010 (26) Older Adults	Cana 300 mg	229	58.5	30.5	21.5;39.5	<0.001
	Cana 100 mg	239	47.7	19.7	10.7;28.7	<0.001
	Placebo	232	28.0			
DIA3004 (26) Moderate Renal Impairment	Cana 300 mg	89	32.6	15.3	1.6;29.0	0.017
	Cana 100 mg	88	27.3	10.0	-3.3;23.4	0.227
	Placebo	87	17.2			
DIA3008 (18) SU substudy	Cana 300 mg	39	33.3	28.3	9.5;47.1	0.004
	Cana 100 mg	40	25.0	20.0	2.5;37.5	0.014
	Placebo	40	5.0			
DIA3008 (18) Insulin substudy	Cana 300 mg	572	24.7	17.0	12.6;21.4	<0.001
	Cana 100 mg	551	19.8	12.1	7.8;16.3	<0.001
	Placebo	545	7.7			

Non Glycemic Secondary Endpoints:

Percent change in body weight from baseline

Canagliflozin causes intravascular volume loss and augments urinary glucose excretion which results in urinary caloric loss. The applicant measured the impact of volume loss and daily caloric loss on body weight over time across all phase 3 trials. Percent body weight change from baseline was a pre-specified key secondary endpoint. The statistical analysis plans for each trial implemented appropriate measures to control Type-1 error across these secondary analyses.

Body weight was to be measured using a calibrated scale at each trial visit. Each study center was responsible for calibrating the scale before weighing the first subject and at 12-week intervals during the trial. Calibration was to be documented in a dedicated log. Subjects were to be weighed at approximately the same time of day on the same scale, on an empty bladder, wearing underwear, a gown and no shoes.

Table 7: Change in body weight from baseline (%) to end of trial

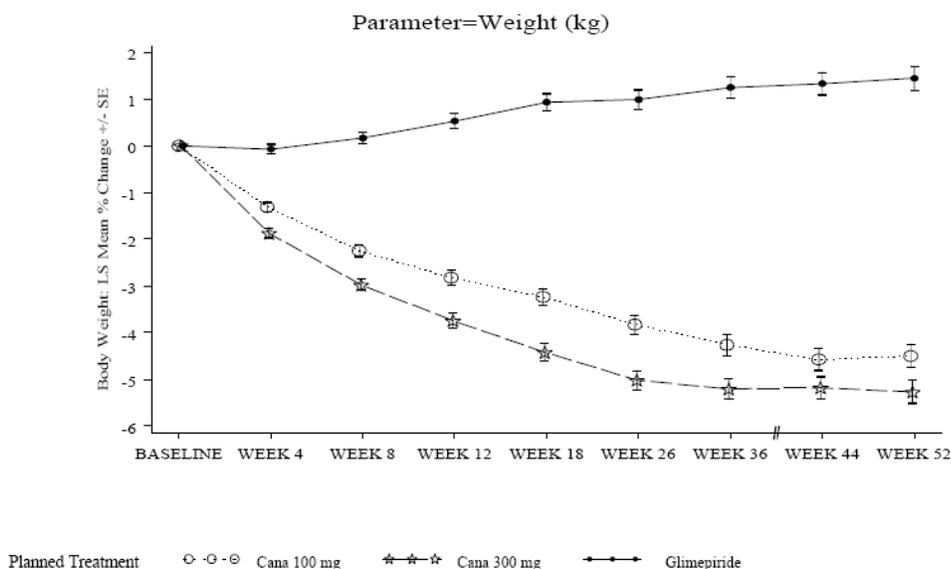
Study (Weeks)	Treatment Arm	N	Baseline Mean (SD), kg	% Change ± SE	LS mean difference (95% CI)	p-value
Monotherapy						
DIA3005 (26) Main study	Canagliflozin 300 mg	194	86.9 (20.6)	-3.9 ± 0.2	-3.3 (-4.0, -2.6)	<0.001
	Canagliflozin 100 mg	192	85.9 (21.5)	-2.8 ± 0.2	-2.2 (-2.9, -1.6)	<0.001
	Placebo	190	87.5 (19.4)	-0.6 ± 0.2		
Add-on to background metformin						
DIA3006 (26) Add-on to metformin	Canagliflozin 300 mg	360	85.4 (20.7)	-4.2 ± 0.2	-2.9 (-3.5, -2.3)	<0.001
	Canagliflozin 100 mg	365	88.7 (22.3)	-3.7 ± 0.2	-2.5 (-3.1, -1.9)	<0.001
	Placebo	181	86.7 (22.5)	-1.2 ± 0.3		
DIA3009 (52) Add-on to metformin	Canagliflozin 300 mg	480	86.6 (19.3)	-4.7 ± 0.2	-5.7 (-6.2, -5.1)	
	Canagliflozin 100 mg	479	86.8 (20.0)	-4.2 ± 0.2	-5.2 (-5.7, -4.7)	
	Glimepiride	478	86.6 (19.8)	1.0 ± 0.2		
Add-on to dual combination therapy						
DIA3002 (26) Add on to metformin+SU	Canagliflozin 300 mg	152	93.5 (22.1)	-2.6 ± 0.3	-2.0 (-2.7, -1.3)	<0.001
	Canagliflozin 100 mg	155	93.5 (22.4)	-2.1 ± 0.3	-1.4 (-2.1, -0.7)	<0.001
	Placebo	150	90.8 (22.5)	-0.7 ± 0.3		
DIA3012 (26) Add on to metformin+PIO	Canagliflozin 300 mg	112	94.4 (26.0)	-3.8 ± 0.3	-3.7 (-4.6, -2.8)	<0.001
	Canagliflozin 100 mg	113	94.2 (22.2)	-2.8 ± 0.3	-2.7 (-3.6, -1.8)	<0.001
	Placebo	114	94.0 (22.4)	-0.1 ± 0.3		
DIA3015 (52) Add on to metformin+SU	Canagliflozin 300 mg	375	87.6 (23.2)	-2.5 ± 0.2	-2.8 (-3.3, -2.2)	<0.001
	Sitagliptin	367	89.6 (23.1)	0.3 ± 0.2		
Special Population						
DIA3010 (26) Older Adults	Canagliflozin 300 mg	229	88.8 (17.1)	-3.1 ± 0.3	-3.0 (-3.5, -2.4)	<0.001
	Canagliflozin 100 mg	240	88.4 (15.6)	-2.4 ± 0.3	-2.3 (-2.8, -1.7)	<0.001
	Placebo	234	91.3 (17.5)	-0.2 ± 0.3		
DIA3004 (26) Moderate Renal Impairment	Canagliflozin 300 mg	89	90.2 (18.1)	-1.5 ± 0.3	-1.8 (-2.6, -1.0)	<0.001
	Canagliflozin 100 mg	90	90.5 (18.4)	-1.3 ± 0.3	-1.6 (-2.3, -0.8)	<0.001
	Placebo	88	92.7 (17.5)	0.3 ± 0.3		
DIA3008 (18) SU substudy	Canagliflozin 300 mg	39	80.4 (19.5)	-2.0 ± 0.5	-1.8 (-3.2, -0.4)	0.014
	Canagliflozin 100 mg	40	85.1 (16.6)	-0.6 ± 0.5	-0.4 (-1.8, 1.0)	0.557
	Placebo	44	85.5 (19.4)	-0.2 ± 0.5		
DIA3008 (18) Insulin substudy	Canagliflozin 300 mg	576	96.7 (20.6)	-2.3 ± 0.1	-2.4 (-2.7, -2.1)	<0.001
	Canagliflozin 100 mg	559	96.9 (21.1)	-1.8 ± 0.1	-1.9 (-2.2, -1.6)	<0.001
	Placebo	551	97.7 (22.3)	0.1 ± 0.1		

The mean percent change in body weight from baseline and the comparator adjusted differences to end of trial are shown for each individual trial in the table above (source: Table 17 in Dr. Kwon's review). Dr. Liu confirmed the applicant's findings in both the mITT population using LOCF as well as the per protocol population (see tables for individual studies in his review). Canagliflozin use was associated with a

0.4-3.3% placebo adjusted percent reduction in body weight from baseline to end of study. A modest dose response is evident. The smallest reduction was seen in the add-on to sulfonylurea study for the 18-week time point. Conclusions based on mean percent weight loss analyses were consistent with analyses based on proportion of individuals who lost > 5% body weight.

The weight loss time course (mITT population LOCF) is shown in each individual study report. For each study, weight loss is evident early (as early as four weeks), is near maximum at 26 weeks and either continues to decline slightly or remains stable at this new level thereafter and until a maximum follow-up period of 52 weeks (trials DIA3009 and DIA3015). A representative example is shown below.

Figure 6: Change in body weight (%) over time. DIA3009 mITT LOCF Source ISR figure 9



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Weight loss from canagliflozin likely results from a combination of both volume and caloric loss. In a subgroup of individuals (n/N=312/1450) in trial DIA3009 body composition (i.e., fat mass, lean mass, bone mineral mass) and fat distribution (i.e., visceral versus subcutaneous) were assessed using Dual X-ray Absortometry (DXA) and Computed Tomography (CT) respectively. Participant selection was based on availability of the equipment at the study site. The subgroup of patients who underwent body composition and fat distribution assessment had similar baseline demographics and diabetes characteristics as the full mITT population.

The DXA assessment suggests that total body weight loss associated with canagliflozin use was predominantly due to fat mass loss (-2.51 kg vs. -1.12 kg of fat vs. lean mass loss for the 300 mg dose and -2.89 kg vs. -0.89 kg of fat vs. lean mass loss or the 300 mg dose). The CT assessment suggests that the fat is lost from both

the visceral adipose tissue (VAT) compartment (i.e., 7.3 and 8.1% reduction in “true” VAT measured as the mean of lumbar levels L3-L5 for the 100 and 300 mg dose) and the subcutaneous adipose tissue (SAT) compartment (5.6 and 5.4% reduction in SAT for the 100 and 300 mg dose).

DXA assessment was also carried out in trial DIA3010 (adults) and findings consistent with those of trial DIA3009 were reported (i.e., ~2/3 of the body weight loss seen with canagliflozin use is associated with fat mass loss).

Mean change in systolic blood pressure from baseline

Canagliflozin exerts an osmotic diuretic effect and results in intravascular volume loss. The applicant measured the impact of this effect on blood pressure across all phase 3 trials. The mean comparator adjusted change in systolic blood pressure from baseline to trial end was designated as a key secondary endpoint in most trials. The applicant had appropriately controlled Type 1 error across these analyses.

Blood pressure measurements were obtained after the subject has been in the sitting position for 5 minutes and before any blood sample collection. Blood pressure was assessed manually with a mercury sphygmomanometer or an automated blood pressure monitor. Three consecutive blood pressure readings were taken and recorded, at intervals of at least 1 minute apart as specified in the trial event schedule.

At the screening visit, blood pressure was to be measured in both arms. The arm with the higher pressure was chosen when an interarm difference of >10 mmHg in either the systolic or diastolic pressure was found. The same arm was then to be used for each subsequent reading and for all clinic visits. To reduce interobserver variability, it was recommended that blood pressure be measured by the same individual at each trial visit.

Canagliflozin use was associated with a clinically and statistically significant reduction in systolic blood pressure in 7 out of 9 trials. Across the nine trials, the comparator adjusted LS mean decrease from baseline to trial end ranged from -0.1 to -7.9 mmHg in the mITT population using LOCF as the imputation method. Dr. Liu confirmed the applicant’s findings in this population and in the per protocol population. An example of the time course for the systolic blood pressure effect is shown in Figure 11 of Dr. Kwon’s review. The decrease in systolic blood pressure is apparent early and was shown to persist out to at least 52-weeks.

Table 8: Change in SBP from baseline to endpoint (mITT LOCF population)

Study (Weeks)	Treatment Arm	N	Baseline Mean (SD)	Change from baseline \pm SE	LS mean difference (95% CI)	p-value
Monotherapy						
DIA3005 (26) Main study	Cana 300 mg	195	128.5 (12.7)	-5.0 \pm 0.8	-5.4 (-7.6, -3.3)	<0.001
	Cana 100 mg	192	126.7 (12.5)	-3.3 \pm 0.8	-3.7 (-5.9, -1.6)	<0.001
	Placebo	190	127.7 (13.7)	+0.4 \pm 0.8		
Add-on to background metformin						
DIA3006 (26) Add-on to metformin	Cana 300 mg	360	128.7 (13.0)	-5.1 \pm 0.6	-6.6 (-8.5, -4.7)	<0.001
	Cana 100 mg	365	128.0 (12.7)	-3.8 \pm 0.6	-5.4 (-7.3, -3.4)	<0.001
	Placebo	181	128.1 (12.7)	+1.5 \pm 0.8		
DIA3009 (52) Add-on to metformin	Cana 300 mg	480	130.0 (13.8)	-4.6 \pm 0.6	-4.8 (-6.2, -3.4)	
	Cana 100 mg	479	130.0 (12.4)	-3.3 \pm 0.6	-3.5 (-4.9, -2.1)	
	Glimepiride	478	129.5 (13.5)	+0.2 \pm 0.6		
Add-on to dual combination therapy						
DIA3002 (26) Add on to metformin+SU	Cana 300 mg	154	130.8 (12.8)	-4.3 \pm 1.0	-1.6 (-4.1, -0.9)	0.201
	Cana 100 mg	156	130.4 (13.5)	-4.9 \pm 1.0	-2.2 (-4.7, 0.2)	0.077
	Placebo	150	130.1 (13.7)	-2.7 \pm 1.0		
DIA3012 (26) Add on to metformin+PIO	Cana 300 mg	112	126.7 (12.0)	-4.7 \pm 1.0	-3.5 (-6.3, -0.6)	0.016
	Cana 100 mg	113	126.4 (12.3)	-5.3 \pm 1.0	-4.1 (-6.9, -1.3)	0.005
	Placebo	114	128.2 (12.3)	-1.2 \pm 1.0		
DIA3015 (52) Add on to metformin+SU	Cana 300 mg	375	131.2 (13.2)	-5.1 \pm 0.7	-5.9 (-7.6, -4.2)	<0.001
	Sitagliptin	367	130.1 (14.0)	+0.9 \pm 0.7		
Special Population						
DIA3010 (26) Older Adults	Cana 300 mg	234	131.1 (14.6)	-6.9 \pm 1.1	-7.9 (-10.1, -5.6)	<0.001
	Cana 100 mg	240	130.6 (13.2)	-3.5 \pm 1.0	-4.6 (-6.9, -2.4)	<0.001
	Placebo	234	131.4 (12.2)	+1.1 \pm 1.0		
DIA3004 (26) Moderate Renal Impairment	Cana 300 mg	89	136.7 (15.0)	-6.4 \pm 1.5	-6.1 (-9.9, -2.3)	0.002
	Cana 100 mg	90	135.9 (13.1)	-6.1 \pm 1.5	-5.7 (-9.5, -1.9)	0.003
	Placebo	88	132.1 (13.6)	-0.3 \pm 1.5		
DIA3008 (18) SU substudy	Cana 300 mg	39	133.5 (13.9)	-5.2 \pm 2.4	-1.8 (-8.2, -4.7)	0.588
	Cana 100 mg	40	138.0 (10.2)	-3.5 \pm 2.3	-0.1 (-6.5, 6.2)	0.975
	Placebo	44	137.3 (13.4)	-3.4 \pm 2.2		
DIA3008 (18) Insulin substudy	Cana 300 mg	576	138.2 (16.8)	-6.9 \pm 0.5	-4.4 (-5.8, -2.9)	<0.001
	Cana 100 mg	559	137.0 (16.8)	-5.1 \pm 0.5	-2.6 (-4.1, -1.1)	<0.001
	Placebo	551	138.2 (16.1)	-2.5 \pm 0.5		

• Safety

The number and duration of exposure was greatest in Phase 3 trials and these trials contributed the largest share of safety data in the NDA. In total, 10,285 patients participated in the nine phase 3 trials. 6645 of these were exposed to one of the two canagliflozin doses and 3640 were exposed to placebo or active comparators. Exposure for Phase 3 by dose and by trial using NDA submission data cutoff dates is shown Tables 29 and 30 of Dr. Kwon's review. Approximately 4700, 1200 and 144 individuals were exposed to canagliflozin for 12, 18 and 24 months respectively.

Trials DIA3008, DIA3009, DIA3010 and DIA3006 contributed the most to patient-year exposure. The cardiovascular outcomes trial alone, DIA3008, contributed the most with 2526 patient-years of exposure to canagliflozin and 1234 patient-years of exposure to placebo.

The integrated safety analyses were based on distinct pools of phase 3 trials divided into four datasets referred to as DS1 or “placebo-controlled dataset”, DS2 or “moderate renal impairment dataset”, DS3 or “broad dataset” and DS4 or “longer-term exposure broad dataset”. Each dataset differed by population pooled, number of trials included in the pool and/or data cutoff dates used. The name and distinguishing features of these four datasets are summarized in Table 28 of Dr. Kwon’s review reproduced and slightly adapted to include patient year exposure below.

Table 9: Safety Dataset Description

Dataset Name	Dataset Description	Pooled Trials	Pooled Treatment Groups	Subject years Exposure [∞]	Cutoff Dates
DS1	Placebo-controlled trials	DIA3002, DIA3005, DIA3006 ² , DIA3012	Placebo Cana 100 mg Cana 300 mg All Cana	294 387 388 775	Primary Efficacy Endpoint (i.e., 26 wks.)
DS2	Moderate Renal Impairment Population*	DIA3004 and subgroups from DIA3005, DIA3008, DIA3010	Placebo Cana 100 mg Cana 300 mg All Cana	260 242 261 503	Primary Efficacy Endpoint (i.e., 26 wks.) September 15, 2011 for DIA3008
DS3	Active- and Placebo-controlled trials ³	DIA3002, DIA3004, DIA3005, DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	Comparators Cana 100 Cana 300 All Cana	2273 2261 2205 4466	Primary Efficacy Endpoint [i.e., 26 wks. for all except DIA3009 (52 wks.)] September 15, 2011 for DIA3008
DS4	Active- and Placebo-controlled trials ³	DIA3002, DIA3004, DIA3005, DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	Comparators Cana 100 Cana 300 All Cana	3380 3381 3306 6688	All data collected through to January 31, 2012

Source: ISS, Table 3; Cana=canagliflozin
High glycemic substudy (DIA3005) excluded (reason no control group).

²Sitagliptin treatment group is excluded.

³DIA3015 excluded (reason no canagliflozin 100 mg dose groups)

*baseline 4 variable MDRD eGFR ≥30 to <60 mL/min/1.73m²

[∞]Regardless of use of rescue

Table 10 summarizes the number of patients in datasets 1-3, the mean subject-years of exposure and the mean exposure in weeks for DS 1-3.

Table 10: Exposure for pooled datasets 1-3 (Source January 10th 2013 EMDAC presentation)

	DS1		DS2		DS3	
	All Cana	Placebo	All Cana	Placebo	All Cana	All Non-Cana
Total (N)	1667	646	714	387	6177	3262
Subject-years Exposure	772	274	508	263	4466	2273
Mean exposure (weeks)	24	22	37	35	38	36

Notable, expected, differences in participant baseline characteristics in the pooled datasets were related to age, disease duration, presence of microvascular diabetes complications at baseline and renal function. Note that baseline characteristics in DS4 are identical to those of DS3. The table immediately below summarizes some of these key differences (Source: Dr. Kwon's presentation January 10th EMDAC.)

	DS1	DS2	DS3
Mean Age (years)	57	67	60
Proportion of subjects age 75 or older	2.3%	17.2%	5.2%
Male (%)	50%	58%	58%
Caucasian (%)	72%	78%	73%
Mean BMI (kg/m ²)	32	33	32
Mean HbA1c (%)	8.0	8.1	8.0
Mean duration of diabetes (years)	7.3	15	10.6
Microvascular complications (%)	19%	59%	33%
Mean eGFR (mL/min/1.73m ²)	88.1	48.2	81.3
Proportion with moderate renal impairment (%)	4.2%	100%	13%

The 4-Month Safety Update was received in September 2012. This update had a data cutoff date of July 1, 2012 and included controlled extension data from all eight trials in DS4. As of this new data cutoff date four of eight of these trials had completed parent and extension phases (i.e., DIA3002, DIA3005, DIA3006 and DIA3012). The total pooled cumulative exposure for the updated DS4 dataset was 4076, 3897, and 4024 patient-years of exposure for canagliflozin 100 mg, 300 mg and comparator, respectively.

My review will focus on DS-4 since it contains the most number of patients exposed and the longest exposure duration of any dataset. Again note that the above exposure estimate for DS4 excludes DIA3015 (i.e., ~ 308 and 300 patient-years of exposure to canagliflozin 300 mg and sitagliptin 100 mg, respectively) and the High Glycemic Substudy in DIA3005 (21 and 19 patient-years of exposure to canagliflozin 100 mg and 300 mg, respectively).

Deaths:

Specific causes of death were generally balanced between the treatment groups and no apparent adverse event or dose-related pattern emerged.

At the time of NDA submission 0.6% (n/N=35/6177) and 0.8% (n/N=26/3262) of participants randomized to canagliflozin and comparator group, respectively, had a treatment-emergent event that resulted in death in DS-4 (source integrated safety summary table 72). As of the 4-Month Safety Update the total number of fatal events in DS-4 was updated to 49 (0.8%) and 37 (1.1%) in the canagliflozin and comparator groups, respectively. These estimates exclude two deaths due to respiratory and cardiac arrest in DIA3015 (see narratives for subjects 150018 and 150162 on pages 104-105 of Dr. Kwon's review). These estimates also exclude deaths that qualified as a primary endpoint in Trial DIA3008.

The majority of treatment-emergent deaths occurred in DIA3008 [i.e., 27/35 and 19/26 in DS-4 (source: reviewer's own analysis of ADAE.xpt dataset)].

Data which follow represent the pool of the two canagliflozin doses (i.e., 2:1 randomization canagliflozin: comparator). Most adverse events preferred term associated with an outcome of death were in the cardiac disorders (12 vs. 9; canagliflozin vs. comparator), general disorders and administration site conditions (5 vs. 4; canagliflozin vs. comparator), nervous systems disorders (6 vs. 4; canagliflozin vs. comparator), and respiratory, thoracic and mediastinal disorders (5 vs. 2 canagliflozin vs. comparator) system organ classes.

Events in the cardiac disorders class were related to terms associated with coronary artery disease, heart failure and or arrhythmia. Events in the general disorders and administration site conditions class were related to cardiac or sudden death. Events in the nervous systems disorders were related to cerebrovascular disease or stroke. Events in the respiratory, thoracic and mediastinal disorders were related to respiratory distress or failure. No fatal outcomes was associated with a term suggestive of a direct, potentially, fatal drug related toxicity. One case of fatal hepatitis was ischemic in origin and associated with multi-organ failure in the context of septic shock secondary to pneumonia (**DIA3005-ID#500529**).

The applicant only provided narratives for deaths occurring up to the efficacy endpoint cutoffs for glycemic efficacy trials and July 21 2011 for trial DIA3008. Line listings

were provided for all other fatal outcomes. Dr. Kwon summarized the 27 canagliflozin associated death narratives which were provided and reviewed the line listing for the rest. Preferred terms in the provided line listings were found to be consistent with the pattern of events from reviewed narratives and no additional narratives were sought.

A clear relationship to canagliflozin to suggest direct drug causality could not be established in the majority of narratives reviewed. Patients who had fatal outcomes on canagliflozin had multiple risk factors or co-morbid conditions known to be associated with the adverse event that precipitated death. No temporal or dose related patterns are evident.

Dr. Kwon identified two treatment emergent deaths where canagliflozin use may have at least contributed to the fatal event.

DIA3009-ID#900882-Anemia-canagliflozin 300 mg: This case describes a 35-year-old Asian woman with a significant past medical history of microalbuminuria, mild anemia (Hgb ~11 g/dL) and mild renal impairment (eGFR at baseline 72 mL/min/1.73m²). On Day 309, the patient was noted to have had worsening renal function marked by a rise in serum creatinine (eGFR of 39 mL/min/1.73m²). No precipitating events to explain this rise are otherwise described. The investigator diagnosed chronic renal failure and considered this event severe in intensity and probably related to study drug. The subject did not receive any other additional treatments and no action was taken with the study medication. The patient was withdrawn from the study on Day 343. The patient's renal function was stable on a repeat evaluation (eGFR 39 mL/min/1.73m²) on Day 344. Her anemia which was mild at baseline also worsened (Hgb 9.5 g/dL). On Day 351 she was treated with ferrous sulfate (no work-up is included to suggest iron deficiency). On Day 371, the subject experienced weakness and was hospitalized. Laboratory test performed on Day 374 revealed worsening anemia (Hgb 5.1 g/dL) and renal function (eGFR 24 mL/min/1.73 m²). On Day 375, the subject developed cardiopulmonary arrest and died on the same day due to the event of anemia. The investigator suspected the cause of death to be myocardial infarction, severe anemia, chronic kidney disease, and T2DM. Renal failure was also considered as a risk factor. At the time of death, the event of renal failure chronic was reported as not resolved.

Reviewer comment: *This subject had moderate renal impairment at baseline marked by decreased eGFR and proteinuria. Although the case history could represent natural progression of the underlying renal disease, irreversible loss of renal function occurred while the patient was on canagliflozin and no other potential causes of kidney injury were identified in the narrative. The fatal outcome was directly linked to worsening renal failure.*

DIA3008-ID# (b) (4) -Hemorrhagic Pancreatitis-canagliflozin 100 mg:

This case describes a 63 year old US male with diabetes and a past medical history significant for coronary artery disease, diabetic neuropathy, hypertension, hyperlipidemia, deep venous thrombosis, cardiac conduction abnormalities, hypothyroidism and vitamin b12 deficiency who was hospitalized and diagnosed with

mental status changes and hypoxemic respiratory failure on Day 223. On Day 224 the patient was diagnosed with hemorrhagic pancreatitis (diagnosis not otherwise detailed). On Day 235, the subject died due to hemorrhagic pancreatitis, altered mental state, respiratory failure, pulmonary edema and 'neurogenic shock'. It is unknown if an autopsy was performed. The patient was on the following background medication: metformin, insulin premix, atenolol, furosemide, cyanocobalamin, levothyroxine, losartan, polyvidone, simvastatin, warfarin and potassium supplement.

The patient had had an episode of group B-streptococcus septicemia on Day 20 of the study which required hospitalization and treatment with intravenous antibiotics.

Reviewer comment: Dr. Kwon believes this to be drug-related because specific classes of antidiabetics have been associated with an increased risk of pancreatitis and because an imbalance in serious adverse events of pancreatitis was identified in the canagliflozin program. The usefulness of this narrative is limited. First, prodromal symptoms and signs are absent from the narrative and it is therefore not possible to establish whether pancreatitis was the primary event or the result of a secondary problem (e.g., abdominal ischemia). The fact that the event was seen > 200 days after initiation of canagliflozin is not consistent with a drug-induced etiology. The presence of medications associated with drug-induced pancreatitis (i.e., furosemide and losartan) further confounds a drug causality assessment.

An additional death was reported in a patient diagnosed on Day 42 of trial DIA2003 (18-week trial not included in original NDA submission) with colon cancer and who died of complications from the disease 201 days later. Colon cancer was in all likelihood present but not diagnosed at baseline and this death is unlikely to be drug related.

No fatal outcomes was associated with a term suggestive of a direct, potentially, fatal drug related toxicity. One case of fatal hepatitis was ischemic in origin and associated with multi-organ failure in the context of septic shock secondary to pneumonia (DIA3005-ID#500529).

Serious Adverse Events:

At the time of NDA submission 10.7% (n/N=659/6177) and 11.6% (n/N=377/3262) of participants randomized to canagliflozin and comparator group, respectively, had at least one treatment-emergent serious adverse event (SAE) in DS-4 (source integrated safety summary table 77). Greater than 50% of the SAE cases occurred in the cardiovascular outcomes trial DIA3008 (349 and 174 events in the canagliflozin and comparator arms respectively). Events which qualified as primary endpoints in DIA3008 were not counted as SAEs.

Incidence across classes was similar. The organ classes with the greatest number of incident cases were: the infections and infestations class [115 (1.9%) versus 76 (2.3%); canagliflozin vs. comparator), the cardiac disorders class [113 (1.8%) vs. 85

(2.6%); canagliflozin vs. comparator], the gastrointestinal disorders class [68 (1.1%) vs. 33 (1.0%); canagliflozin vs. comparator], injury poisoning and procedural complications [62 (1.0%) vs. 34 (1.0%); canagliflozin vs. comparator) and the nervous system disorders class [60 (1.0%) vs. 34 (1.0%); canagliflozin vs. comparator].

The majority of events in the infectious disease disorders class were related to the medical concepts of pneumonia, urinary tract infection, cellulitis, osteomyelitis, gastroenteritis and lower respiratory tract infection. The majority of events in the cardiac disorders class were related to coronary artery disease, arrhythmia cardiac heart failure or cardiac arrest. The majority of events in the gastrointestinal disorders class were related to abdominal pain, hernia, gastrointestinal motility disorder and gastro-intestinal bleed. The majority of events in the injury poisoning and procedural complications class were related to bone fractures, joint disorder and wound disorders. Events in the nervous systems disorders were related to cerebrovascular disease, syncope and loss of consciousness. Risk factors for many of these disorders were highly prevalent in the population studied (e.g., advancing age, diabetes, obesity, hypertension, atherosclerotic cardiovascular disease, osteoporosis).

Incidence of individual serious adverse event preferred terms reported were generally balanced and each event occurred rarely. No single individual terms occurred at an incidence of > 0.4%. The most frequently reported term was 'coronary artery disease'.

To identify potentially drug related SAEs from the more than 1000 serious adverse event cases, I extracted treatment emergent SAE preferred terms which occurred ≥ 1.5 times more frequently on canagliflozin than on comparators. This analysis was based on data in the ADAE.xpt dataset submitted to support the integrated safety summary and is based on total event counts and not incident cases (i.e., sponsor's analysis). The search revealed 30 imbalanced preferred terms listed in Figure 7 below. The count data retrieved using this search strategy are generally consistent with the numbers based on incident cases and shown by the sponsor on Table 77 of the integrated summary of safety (refer to Page 196 of the ISS). All terms where the risk increased or remained unchanged after addition of 4-MSU data are highlighted in yellow in Figure 8.

For any specific terms imbalances occurred at low incidence (i.e., < 1%) and in most cases were driven by fewer than 10 patients. Splitting is evident for several terms (e.g., Cholecystitis acute, cholecystitis and cholecystitis infective).

Figure 7: Serious Adverse Event Preferred Terms Appearing 1.5-Fold More Frequently in All Cana group (DS-4 Cutoff NDA submission)

MedDRA Preferred Term	All Comparators (n)	Proportion (%) All Comparators (n/ 3262* 100)	All Cana (n)	Proportion (%) All Cana (n/ 6177* 100)	Cana/ Comparator
Peripheral ischaemia	1	0.03	9	0.15	4.8
Inguinal hernia	1	0.03	6	0.10	3.2
Osteomyelitis	2	0.06	10	0.16	2.6
Breast cancer	1	0.03	5	0.08	2.6
Arthralgia	1	0.03	5	0.08	2.6
Osteoarthritis	4	0.12	19	0.31	2.5
Diabetic foot	2	0.06	8	0.13	2.1
Peripheral arterial occlusive disease	2	0.06	8	0.13	2.1
Cholecystitis acute	1	0.03	4	0.06	2.1
Gastrointestinal haemorrhage	1	0.03	4	0.06	2.1
Haematuria	1	0.03	4	0.06	2.1
Diabetic ketoacidosis	1	0.03	4	0.06	2.1
Spinal osteoarthritis	1	0.03	4	0.06	2.1
Cardiac failure congestive	4	0.12	15	0.24	2.0
Pulmonary embolism	2	0.06	7	0.11	1.8
Prostate cancer	2	0.06	7	0.11	1.8
Renal impairment	3	0.09	10	0.16	1.8
Cerebrovascular accident	3	0.09	10	0.16	1.8
Cholecystitis	2	0.06	6	0.10	1.6
Skin ulcer	2	0.06	6	0.10	1.6
Back pain	2	0.06	6	0.10	1.6
Coronary artery stenosis	2	0.06	6	0.10	1.6
Humerus fracture	1	0.03	3	0.05	1.6
Pancreatitis	1	0.03	3	0.05	1.6
Vertebrobasilar insufficiency	1	0.03	3	0.05	1.6
Intermittent claudication	1	0.03	3	0.05	1.6
Mental status changes	1	0.03	3	0.05	1.6
Angina unstable	3	0.09	9	0.15	1.6
Hypoglycaemia	3	0.09	9	0.15	1.6
Atrial fibrillation	6	0.18	17	0.28	1.5

Figure 8: Serious Adverse Events Identified above using 4-Month Safety Update Cutoff (Source: page 191 4-MSU)

MedDRA Preferred Term	All Comparators (n)	Proportion (%) All Comparators (n/ 3262* 100)	All Cana (n)	Proportion (%) All Cana (n/ 6177* 100)	Cana/ Comparator
Peripheral ischaemia	2	0.06	10	0.16	2.6
Inguinal hernia	1	0.03	6	0.10	3.2
Osteomyelitis	2	0.06	12	0.19	3.2
Breast cancer	2	0.06	7	0.11	1.8
Arthralgia	1	0.03	5	0.08	2.6
Osteoarthritis	5	0.15	21	0.34	2.2
Diabetic foot	2	0.06	10	0.16	2.6
Peripheral arterial occlusive disease	3	0.09	7	0.11	1.2
Cholecystitis acute	1	0.03	7	0.11	3.7
Gastrointestinal haemorrhage	1	0.03	8	0.13	4.2
Haematuria	1	0.03	5	0.08	2.6
Diabetic ketoacidosis	1	0.03	4	0.06	2.1
Spinal osteoarthritis	1	0.03	4	0.06	2.1
Cardiac failure congestive	9	0.28	12	0.19	0.7
Pulmonary embolism	5	0.15	10	0.16	1.1
Prostate cancer	1	0.03	9	0.15	4.8
Renal impairment	3	0.09	10	0.16	1.8
Cerebrovascular accident	4	0.12	12	0.19	1.6
Cholecystitis	3	0.09	7	0.11	1.2
Skin ulcer	2	0.06	9	0.15	2.4
Back pain	1	0.03	4	0.06	2.1
Coronary artery stenosis	2	0.06	6	0.10	1.6
Humerus fracture	1	0.03	3	0.05	1.6
Pancreatitis	1	0.03	2	0.03	1.1
Vertebrobasilar insufficiency	1	0.03	5	0.08	2.6
Intermittent claudication	1	0.03	5	0.08	2.6
Mental status changes	1	0.03	3	0.05	1.6
Angina unstable	12	0.37	21	0.34	0.9
Hypoglycaemia	4	0.12	10	0.16	1.3
Atrial fibrillation	8	0.25	18	0.29	1.2

A risk ratio could not be calculated for preferred terms where zero events occurred in the control group. I reviewed these preferred terms manually. Four preferred terms appeared at least four times in the canagliflozin group versus never in the control group. These were 'benign prostatic hyperplasia' (5 vs. 0 events), 'phimosis' (4 vs. 0 events), 'small intestinal obstruction' (4 vs. 0) and 'urticaria' (4 vs. 0). Serious adverse events of 'urticaria' and 'phimosis' will be discussed in dedicated sections. Benign prostatic hyperplasia cases were hospitalizations for symptomatic relief of bladder obstruction or for surgical interventions (i.e., prostatectomy).

Only one narrative is included for small intestinal obstruction ([REDACTED] (b) (4)) and describes a 61 year old male with a past surgical history significant for colectomy 10 years prior to trial initiation who had two episodes of small intestinal obstruction on Days 272 and 457. The previous history of intra-abdominal surgery puts this patient at risk for small intestinal obstruction. Another case of small intestinal obstruction not counted as a part of DS-4 was seen in Trial 3015 on a patient with a known ventral hernia randomized to sitagliptin. The imbalance in small intestinal obstruction is based on few incident cases and is likely a chance finding.

'Peripheral Ischaemia': I reviewed 4 provided narratives which occurred in the canagliflozin group [ID# (onset Day): [REDACTED] (b) (4) (Day 265), [REDACTED] (b) (4) (Day 49), [REDACTED] (b) (4) (Day 212), [REDACTED] (b) (4) (Day 155)]. All represented hospitalization for lower extremity digit necrosis necessitating medical or surgical intervention. In addition to diabetes, all patients had either established peripheral vascular or cardiovascular disease or known risk factors for these conditions. No temporal or dose response pattern is evident from the totality of cases.

'Osteomyelitis': I reviewed 5 provided narratives which occurred in the canagliflozin group [ID# (onset Day): [REDACTED] (b) (4) (Day 156 and Day 270), [REDACTED] (b) (4) (Day 435), [REDACTED] (b) (4) (Day 73), [REDACTED] (b) (4) (Day 324), [REDACTED] (b) (4) (Day 106)]. All represented hospitalization for complications associated with a diabetic foot infection. Presence of predisposing comorbid conditions and risk factors characterized all cases. No temporal or dose response pattern was seen.

'Gastrointestinal Haemorrhage': I reviewed 3 provided narratives which occurred in the canagliflozin group [ID# (onset Day): [REDACTED] (b) (4) (Day 360), [REDACTED] (b) (4) (Day 111), [REDACTED] (b) (4) (Day 50)]. All represented hospitalization for symptomatic gastrointestinal bleeds. Two were upper gastrointestinal bleeds (UGI) and one was a lower gastrointestinal bleed (LGI). The first patient with an UGI bleed had a known history of gastric ulcer, gastritis and duodenitis, the second patient had a history of "clipping stomach vessel" and was diagnosed with a Dieulafoy lesion while in the trial. The patient with the lower GI bleed was diagnosed with diverticular disease on CT-scan. No temporal or dose response pattern was seen.

'Arthralgia': I reviewed 4 provided narratives which occurred in the canagliflozin group [ID# (onset Day): [REDACTED] (b) (4) (Day 14 and 188), [REDACTED] (b) (4) (Day 169), [REDACTED] (b) (4) (Day 224), [REDACTED] (b) (4) (Day 330)]. All represented hospitalization for known pre-existing conditions

of arthralgia or arthritis; at least two represented hospitalization for surgical intervention to ameliorate the known condition.

'Osteoarthritis': I reviewed 5 provided narratives for events in the canagliflozin group [ID# (onset Day): 501165 (Day 106), (b) (4) (also Day 106) (b) (4) (Day 415), (b) (4) (Day 228), (b) (4) (Day 288)]. All five narratives represented events of hospitalization for total knee replacement or knee arthroplasty in patients with known arthritis at baseline.

'Prostate Cancer': Only three narratives were provided in the NDA and are summarized below.

- **DIA3008-ID#** (b) (4): 64 year old Asian man with known benign prostatic hyperplasia. Patient was randomized to canagliflozin 300 mg and diagnosed with prostate cancer on Day 50 following a transurethral resection of the prostate for an elevated prostate specific antigen (PSA).
- **DIA3008-ID#** (b) (4): 74 year old man from Canada diagnosed with prostate cancer "approximately 1.5 months post randomization" (diagnosis not otherwise described). On Day 120 a biopsy was performed to evaluate prostate cancer. Patient was treated with complete androgen blockade.
- **DIA3010-ID#** (b) (4): 61 year old man with a history of elevated PSA was randomized to canagliflozin 100 mg diagnosed after biopsy for a rise in PSA to 9.3 ng/mL. Patient had a prostatectomy on Day 209.

Line listings for the following cases were provided in the NDA.

- **DIA3005-ID#500170**: 65 year old randomized to canagliflozin 100 mg diagnosed on Day 354. No narrative.

Requested narrative received on 3/6/2012: Subject had a baseline elevated PSA of 3.9 ng/mL. Subject underwent a prostate biopsy on Day 354 for a PSA of 3.2 ng/mL and was diagnosed with prostate cancer on the same day. No treatment was administered.

- **DIA3008-ID#** (b) (4): 74 year old randomized to canagliflozin 100 mg diagnosed on Day 166. No narrative

Requested narrative received on 3/6/2012: Subject had a baseline history of benign prostatic hyperplasia. The subject diagnosed with elevated PSA (4.24 ng/mL) on routine labs. Prostate biopsy performed on Day 152. Prostate cancer diagnosed on Day 166.

- **DIA3008-ID#** (b) (4): 65 year old randomized to canagliflozin 100 mg diagnosed on Day 150. No narrative.

Requested narrative received on 3/6/2012: Subject had a baseline history of benign prostatic hyperplasia. Subject diagnosed with elevated PSA (6.9 ng/mL) on an unspecified date. Subject underwent a prostate biopsy and was diagnosed with prostate cancer on Day 152. On Day 235 the subject underwent a radical prostatectomy. The biopsy revealed two small foci of non-invasive prostate cancer.

- **DIA3006-ID#601632**: 59 year old randomized to canagliflozin 300 mg diagnosed on Day 203. No narrative.

Requested narrative received on 3/6/2012: On Day 184 the subject visited a urologist for a 'urological problem' not otherwise specified. On Day 196 benign prostatic hyperplasia was diagnosed. On Day 205 the subject underwent a prostate biopsy which revealed prostate carcinoma (reason for biopsy not otherwise specified). Histopathology confirmed grade III adenocarcinoma.

- **DIA3008-ID#** [REDACTED] (b) 57 year old randomized to canagliflozin 300 mg diagnosed on Day 425. No narrative.

Requested narrative received on 3/6/2012: Patient had no past medical history of prostate issues. Subject presented with weak urine stream, hesitancy and post-micturitional dribbling. The patient was diagnosed with a prostate lesion on digital rectal exam at an unspecified date. The patient underwent a prostate biopsy on Day 425 and was diagnosed with a Gleason 6 prostatic adenocarcinoma of the right lobe.

- **DIA3008-ID#** [REDACTED] (b) (4): 66 year old randomized to canagliflozin 300 mg diagnosed on Day 329. No narrative.

Requested narrative received on 3/6/2012: 66 year old man with no prior prostate issues. On Day 245 the subject was found to have an elevated PSA. Patient was referred to a urologist for dysuria Day 251. A suspicious lesion found on prostate ultrasound. Prostate biopsy performed on Day 306 and confirmed diagnosis of prostate carcinoma on day 329. Subject initiated androgen blockade on Day 337.

An information request was issued on 3/3/2012 asking the sponsor to provide updated data on prostate cancer incidence and incidence rate and to include narratives for all serious and non-serious prostate cancer cases.

The applicant responded to our request on 3/6/2012. 12 (0.3%) cases of prostate cancers were identified in the all canagliflozin group versus 6 (0.3%) in the comparator group as of December 31 2012 (refer to Figure 9). Incidence rates per male patient year exposure are similar for the canagliflozin and comparator groups. The applicant notes that the incidence rate of 2-3 cases per 1000 patients treated for a year is similar to the incidence rate observed in a pooled safety analysis of 19 double-blind clinical trials evaluating sitagliptin¹. The slight increased incidence in the 300 mg canagliflozin dose group is driven by two excess cases and slightly shorter exposure duration.

I reviewed the six cases occurring on comparators. Case histories and latencies were similar to the above reviewed canagliflozin cases. I also reviewed cases not coded as 'serious' adverse events. Case histories for these were similar to the above reviewed cases.

Reviewer comment: *The 9:1 (4.5:1 corrected for randomization) imbalance in serious adverse event of prostate cancer noted at the 4 Month Safety Update appears to be a chance finding. This imbalance was not seen if both serious and non-serious adverse events were*

¹ Williams-Herman D (2010), Engel SS, Round E, et al. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. BMC Endocrine Disorders 2010;10:7.

pooled at that time point. The case narratives between serious and non-serious events do not appear to signal more aggressive disease but simply investigator variability in coding the event. Most cases appeared to be discovered incidentally after measurement of PSA. The short latency of ~6 months or less for ~50% of the cases is not consistent with a drug related tumorigenic mechanism. Given the fact that canagliflozin is associated with mycotic and urinary tract infections and that at least some of the symptoms for these disorders overlap with symptoms of prostate enlargement, it is not unreasonable to suspect that detection bias (i.e., referral to urology) could play a role in apparent imbalance in prostate events with this drug class. This is a moot point given the fact that no differences in sex-specific incidence rates were found as of the latest update.

Figure 9: Incident Prostate Cancer Cases (Data cutoff December 31 2012; Response to information request 3/3/3012)

Table 2: Incidence of Prostate Cancer Through 31 December 2012
 (ISS DS3-LT3 - FDA Request: Safety Analysis Set)

	Cana 100 mg (N=1803)	Cana 300 mg (N=1766)	All Cana (N=3569)	All Non-Cana (N=1924)	Cana 100 mg minus All Non-Cana		Cana 300 mg minus All Non-Cana		All Cana minus All Non-Cana	
					Diff ^a	95%CI ^b	Diff ^a	95%CI ^b	Diff ^a	95%CI ^b
n (%) with at least 1 adverse event of prostate cancer	4 (0.2)	8 (0.5)	12 (0.3)	6 (0.3)	-0.1	(-0.5; 0.3)	0.1	(-0.3; 0.6)	0.0	(-0.3; 0.4)
Incidence rate per 1000 person-years exposure (SE) ^c	1.37 (0.03)	2.87 (0.07)	2.10 (0.04)	2.08 (0.05)	-0.7	(-3.11; 1.68)	0.8	(-2.02; 3.59)	0.0	(-2.19; 2.23)
Male subject-year exposure	2921.3	2787.7	5709.0	2878.3						

^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 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.

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: 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.

'Cholecystitis Acute' and 'Cholecystitis': Serious adverse events of cholecystitis were more commonly observed with canagliflozin (~1.6 X more common in cana versus comparator group when both terms are combined and incident cases are considered). The overall imbalance did not disappear with addition of 4 Month-Safety-Update data (risk ratio ~ 1.8 X more common in cana versus comparator group when both terms are combined). I reviewed 9 provided narratives

ID# (dose; onset day; prior hepato-biliary disorder):

- 120205 (Cana 100; Day 181; prior on trial LFT increase)
- (b) (4) (Cana 300; Day 451; prior on trial LFT increase)
- 902279 (Cana 300; Day 311; prior on trial LFT increase)
- 602815 (Cana 300; Day 92)
- 200073 (Cana 300; Day 77);
- (b) (4) (Cana 100; Day 21)
- (b) (4) (Cana 100; Day 275)
- (b) (4) (Cana 300; Day 307)
- (b) (4) (Cana 300; Day 382)

All cases represented subjects who received an in-hospital intervention (medical or surgical) for symptoms and signs consistent with cholecystitis. Narratives contained sufficient evidence from laboratory (i.e., leukocytosis) imaging or surgical data to

corroborate the diagnosis in the majority of cases. In several cases gall bladder stones, biliary duct dilatation or cholangitis to suggest antecedent biliary tract obstruction were identified as a risk factor for gallbladder disease. Slightly more cases were observed in the high dose group. Most episodes occurred late after initiation of therapy.

An additional case of gangrenous cholecystitis was coded to the preferred term 'cholecystitis infective' in the infection and infestations disorders class.

- DIA3008-ID# (b) (4) Cholecystitis infective (Day 338): 82 year old man on canagliflozin 300 mg

Reviewer Comment: *Canagliflozin raises serum cholesterol and causes weight loss. These two risk factors could conceivably augment biliary cholesterol secretion and through this mechanism could predispose to gallstone formation. There were no details regarding weight loss or cholesterol levels in the provided narratives. It is biologically plausible that canagliflozin augments one's risk for cholecystitis if it predisposes to gallstone formation. Other theoretical possibility includes interference with entero-hepatic bile acid circulation or motility disorders due to SGLT-1 mediated malabsorption. There appears to be a dose response. Review of these narratives also shows that several of the liver function abnormalities noted were linked to the presence of hepato-biliary stones. I recommend labeling this imbalance.*

'Haematuria': Only one narrative for the canagliflozin group was provided in the NDA [ID# (onset Day): 802009 (Day 119)]. The subject is an 80 year old man from Spain with a history of benign prostatic hyperplasia. The subject presented with gross hematuria on Day 119. The hematuria was attributed to the recent initiation of coumarin therapy. No further work-up is described. The event was considered resolved on Day 122.

'Diabetic Ketoacidosis': I reviewed the following narratives [ID# (onset Day): 150729 (Day 316), (b) (4) (Day 21), (b) (4) (Day 288)]

Subject (b) (4) was a 76 year old man from Australia with a complex past medical history which includes atherosclerotic disease and complicated diabetes treated with insulin. Renal disease is not noted as a known condition in narrative. The subject experienced nausea, diarrhea and vomiting on Day 21. The subject skipped insulin doses and presented with nausea, vomiting, diarrhea and hyperglycemia to hospital the next day. The patient was treated with IV fluid hydration and IV insulin. In hospital, the patient was diagnosed with a non-ST elevation MI based on ST-T changes in left precordial leads and minimal troponin T elevation (~2 fold upper limit of normal). No other vital sign or laboratory data is provided in the narrative.

Reviewer Comment: *Diabetic ketoacidosis is almost never seen in patients with type 2 diabetes. While the symptoms and sign may be consistent with this diagnosis it is more likely that nausea, vomiting, diarrhea and dehydration resulted from a condition other than DKA (i.e., viral gastroenteritis) and followed by skipped insulin doses accounts for the patient*

presentation. The applicant provides no laboratory data to substantiate that the patient had acidemia and or ketonemia. The impact of dehydration on renal function and vitals is not described. In this case volume contraction and metabolic disturbances appeared to have triggered the non-ST MI. While the investigator reported that the MI triggered the DKA the narrative does not invoke symptomatic heart disease before the event.

- Subject (b) (4) was a 75 year old male from the US with a past medical history significant for diabetes and diagnosed with diabetic ketoacidosis and liver function abnormalities (ALT 5X the ULN) when he presented to hospital with a 3-day history of nausea and vomiting and elevated glucose. An acoustic shadow (stone vs. polyp) and bile duct dilatation considered normal for age was noted on gallbladder ultrasound performed during hospitalization. Liver serology for Hepatitis A, B and C were non-reactive. The patient recovered with IV hydration and insulin. Liver enzymes recovered within three days and returned to normal within ~10-15 days.

Reviewer Comment: *This case does not likely represent true diabetic ketoacidosis for the same reasons mentioned above.*

- Subject **150729** was a 58 year old female from Ukraine who presented with right upper costochondral pain, fever and weakness on Day 310. The subject underwent an endoscopic retrograde cholangiopancreatography with sphincterectomy and cholelithotomy Day 316. The patient was diagnosed with 'gallbladder edema' and underwent laparoscopic cholecystectomy which revealed acute on chronic cholecystitis. Subject developed ketonemia on Day 316 and was treated with oral rehydration salts and insulin.

The remaining imbalanced terms will be discussed in dedicated sections.

As of the 4-Month Safety Update the number of incident cases with at least one serious adverse event in DS-4 rose to 823 (13.3%) and 445 (13.6%) in the canagliflozin and comparator groups respectively (source 4 Month Safety Update table 15). No changes in the pattern of serious events were seen.

Adverse Events Leading to Discontinuations:

At the time of NDA submission and in the dataset with the largest and longest duration of exposure (i.e., DS-4) 5.6% (n/N=348/6177) and 4.4% (n/N=142/3262) of participants randomized to the canagliflozin and comparator group respectively discontinued treatment due to an adverse reaction in (source integrated safety summary table 83).

An imbalance not favoring canagliflozin was seen in the: infections and infestations class (1.1% versus 0.5%), investigations class (0.8% versus 0.5%), renal and urinary disorders class (0.6% versus 0.2%), reproductive systems and breast disorders (0.5 versus 0.1%) and general disorders and administration class (0.4% versus 0.1%).

Medical terms capturing the concept of female genital mycotic infections and urinary tract infections accounted for most discontinuations in the infections and infestations class. The preferred terms 'blood creatinine increased' (0.2% vs. 0.1%), 'glomerular filtration rate decreased' (0.2% vs. 0.1%) and weight decreased (0.1% vs. 0%) accounted for most discontinuations in the investigations class. Medical terms capturing increased urination and renal impairment accounted for most discontinuations in the renal and urinary disorders class. Terms capturing male genital mycotic infections accounted for most discontinuations in the reproductive and system and breast disorders class. The preferred term fatigue (10 vs. 0) accounted for most discontinuations in the general disorders and administration site conditions.

Reviewer Comment: *The applicant reviewed cases of discontinuations due to fatigue. Fatigue occurred within 60 days of canagliflozin initiation in 7 out of 10 cases. In three cases fatigue was associated with a UTI or mycotic infection. In two cases fatigue was associated with diuretic related adverse events (dry mouth and thirst). Although direct evidence for this is not provided, it is expected that significant renal impairment and or accompanying electrolyte changes could contribute to fatigue in certain patients. The temporality and association with known side effects of the medication makes this adverse reaction a significant drug related adverse events which should be labeled.*

Common Adverse Events

As of the NDA data cutoff date 74% and 72% of patients in DS-4 had experienced at least one treatment emergent adverse event in canagliflozin and comparator groups respectively (refer to Table 59 in the integrated summary of safety)

Most events were subsumed under the; infections and infestations (40% versus 38%; canagliflozin versus comparators), gastrointestinal disorders (22% versus 20% canagliflozin versus comparators), musculoskeletal and connective tissue disorders (20% vs. 20%), metabolism and nutrition disorders (13% versus 15%), nervous system disorders (15% versus 13%) and general disorders and administration site conditions organ classes.

The most common preferred terms in each of the above categories represented common medical conditions and these were balanced between groups (i.e., nasopharyngitis, diarrhea, arthralgia, hypoglycemia, hyperglycemia, backpain and headaches).

Preferred terms from most to least common, occurring in at least 15 participants on canagliflozin (i.e., 0.3%) and more frequently² on canagliflozin than on comparators included;

- 'Upper respiratory tract infection' (6.1% versus 5.0%),
- Preferred terms associated with the concept of genital mycotic infections (e.g., balanitis, vulvitis etc.) and 'phimosis' (0.3% versus 0.1%),

² 95% CI around the between group difference excludes zero for at least one dose of canagliflozin. (Refer to Table 60 in ISS for details)

- Preferred terms associated with the concept of increased urination: 'pollakiuria' (3.9% versus 1.0%), 'polyuria' (1.0% versus 3.0%), 'urine output increased' (0.6% versus 0.1%)
- Preferred terms associated with the medical concept of increased thirst terms: 'thirst' (1.8% versus 0.1%), 'dry mouth' (0.8% versus 0.4%), 'polydipsia' (0.3% versus 0.1%)
- 'Hypotension' (1.5% versus 0.5%), 'orthostatic hypotension' (0.5% versus 0.1%)
- 'Asthenia' (1.0% versus 0.6%),
- 'Palpitations' (0.6% versus 0.3%)
- 'Cataract' (1.4% versus 0.9%)
- 'Weight decreased' (0.9% versus 0.2%)
- 'Blood creatinine increased' (1.1% versus 0.4%), 'blood urea increased' (0.6% versus 0.3%)
- 'Blood potassium increased' (0.4% versus 0.1%)
- 'Hypercalcemia' (0.3% versus 0.1%)
- 'Skin ulcers' (0.9% versus 0.5%)
- 'Erythema' (0.4% versus 0.2%)
- 'Tremor' (0.4% versus 0.1%)
- 'Skeletal injury' (0.3% versus 0.1%)

With the exception of 'upper respiratory tract infection' and 'cataract' the mechanism of action of canagliflozin or specific toxicity supports a drug-related causality in each of these adverse events.

The applicant has grouped medical terms associated with increased urination and increased thirst into 'osmotic diuresis related adverse events'. These are discussed in Dr. Kwon's review and will not be discussed further here (refer to Tables 42-44 of her review). In summary, a clear strong association between canagliflozin use and occurrence of these symptoms were seen.

Special Safety Issues

Hepatotoxicity:

Hepatotoxicity was not identified as a risk associated with use of canagliflozin that would outweigh its benefit and preclude approval in the more than ~ 8000 patient-year of exposure in the clinical program (i.e., includes exposure up to the 4 Month Safety Update).

A prospective process based on regularly timed medical monitoring of safety laboratory values and reported adverse events terms was set up to capture potentially significant liver injury cases in Phases 1-3. The following events identified through this process were evaluated in a blinded fashion by an independent hepatic event adjudication committee (HEAC) consisting of three physicians with expertise in liver disease.

- ALT or AST elevations $\geq 5x$ ULN
- Combined ALT $\geq 3x$ ULN and total bilirubin $\geq 2x$ ULN
- Any adverse events corresponding to a list of selected / pre-specified liver injury-related preferred terms (see HEAC Charter in Appendix 7)

At the time of NDA submission 56 subjects met adjudication criteria. 50 were referred based on biochemical criteria and six subjects were referred based on preferred term criteria (See Table 86 in Dr. Kwon’s review). No cases on canagliflozin were adjudicated as “probable” or “definite” cases of drug induced liver injury (refer to Dr. Kwon’s review for detailed definitions). 5 out of 43 cases occurring on canagliflozin were judged as representing possible drug induced liver injury [i.e., mostly on the basis of the fact that diagnostic tests were missing to exclude definitely exclude drug induced liver injury (DILI)]. In 38 out of 43 cases occurring on canagliflozin, drug induced liver injury was determined to be unlikely or excluded.

We consulted Dr Seeff a hepatologist from the Office of Surveillance and Epidemiology to review 18 narratives representing cases of severe hepatic enzyme elevation or liver failure. Dr. Seeff did not find a hepatotoxicity signal in the group of narratives reviewed. Several narratives were missing serological and imaging data to rule-in more likely causes of cytolytic or cholestatic liver injury (refer to his review for details).

Biochemical Hy’s Law Cases

As of the 4 Month Safety Update 10 cases in the canagliflozin group versus 2 in the comparator group (one on placebo and glimepiride each) met laboratory criteria for Hy’s Law (ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 ULN) in the Janssen development program. Two additional cases were identified in trials carried out by Mitsubishi Tanabe Pharmaceutical Corporation, the company developing canagliflozin in Japan. These two cases were outside of Janssen’s purview and did not undergo HEAC review. None of the 10 canagliflozin cases reviewed by the HEAC were judged to represent a definite, probable or even a possible case of drug induced liver injury.

We asked Dr. Seeff in OSE to review two challenging cases (see cases* in table below). One case had been reviewed extensively prior to NDA submission by both Dr. Seeff and Dr. John Senior (**Case ID#** (b) (4)) Refer to Dr. Seef’s review for full history of past FDA reviews on this case.

After review of all narratives, we agree and concur with the applicant’s assessment that the narratives were sufficiently detailed to exclude with reasonable certainty drug induced liver injury as the event triggering hepatic enzyme abnormalities in all 12 narratives.

Table 11: Treatment Emergent Biochemical Hy’s Law in Controlled Studies (Cutoff 4 MSU; incident cases in 4 MSU highlighted in grey)

Case ID#	Day Noted (Dose)	Likely Alternative Etiology
400373 (b) (4)	Day 29 (100 mg)	Choledocholithiasis
	Day 281 (100 mg)	Hepatitis E
120205 (b) (4)	Day 180 (100mg)	Choledocholithiasis and cholecystitis
	Day 344 (300 mg)	Obstructive jaundice gastric adenocarcinoma (Stomach)

(b) (4)	Day 276 (100 mg)	Cholangiocarcinoma
150565	Day 176 (300 mg)	Choledocholithiasis
(b) (4)	Day 235 (100 mg)	Dr. Seeff; Likely "idiopathic" sclerosing cholangitis. "extremely low possibility" of canagliflozin induced liver disease
(b) (4)	Day 448 (300 mg)	Dr. Seeff; almost certainly not drug induced canagliflozin hepatotoxicity due to latency and course
(b) (4)	Day 531 (300 mg)	Cholelithiasis and cholecystitis
(b) (4)	Day 554 (Blinded)	Cholelithiasis and cholecystitis
(b) (4) Mitsubishi	Day ~180 (100 mg)	Cholangiocarcinoma
(b) (4) Mitsubishi	Day ~180 (200 mg)	Autoimmune pancreatitis (IgG4); obstructive jaundice

Alanine Aminotransferase: Predefined Limit of Change Analyses

More subjects randomized to canagliflozin were observed to have significant elevation in alanine aminotransferase on pre-defined limit of change analyses in DS-3. Analyses based on AST or a combination of AST and ALT were consistent with these results.

Table 12: Incident Cases (Incidence Rate) with ALT above the predefined limit of change in DS-3 (Source Table 177 ISS)

Alanine Amino Transferase (multiple above normal limit)	Canagliflozin n (n/1000 PYE)	Comparator n (n/1000 PYE)
>3X	35 (7.87)	13 (5.74)
>5X	14 (3.15)	3 (1.33)
>8X	8 (1.80)	1 (0.44)
>10X	5 (1.12)	1 (0.44)
>20X	2 (0.45)	0 (0.00)

I reviewed all cases (i.e. not just the ones from DS-3 shown above) of ALT elevation > 10 X above the upper limit of normal (ULN). Information from case histories were not consistent with DILI and more likely to represent liver injury due;

- Liver ischemia secondary to septic shock (**Case ID#500539**);
- Underlying baseline choledochal disease, hepatic steatosis, poor metabolic control and temporally related to initiation of salsalate therapy³, (**Case ID#500611**). (note; this case had normalization of liver function without de-challenge).
- Acute hepatitis B infection (**Case ID#** (b) (4))
- Liver ischemia due to acute ST-elevation MI (**Case ID#** (b) (4))
- Biliary duct obstruction from cholangiocarcinoma (**Case ID#** (b) (4))
- Acute hepatitis E infection (**Case ID#** (b) (4))
- Case history consistent with laboratory error (**Case ID#** (b) (4))

³ See adverse reaction section of salsalate label and Digestive Diseases and Sciences, Volume 54 (6): 1375-1376– Jun 1, 2009.

- Hepatitis C, cholelithiasis, hepatosteator, alcohol (**Case ID#900990**)
- Case history consistent with sample mix-up with patient ID#900990 (**Case ID# (b) (4)**)

The following two canagliflozin cases lacked serological or imaging data to definitely rule out drug induced liver injury (DILI).

- **Case ID# (b) (4)** is a 70 year old man with Day 1 ALT ~ 9-10 X the ULN (i.e., before first dose of canagliflozin). Scant narrative. Subject continued on study drug and had normalization of liver function while on drug. DILI unlikely given elevation before drug initiation and normalization while on drug.
- **Case ID#902096** is a 73 year old man with hepatosteator and ALT ~ 10 X the ULN on Day 86. Drug was withdrawn.

Mean Percent Change From Baseline in ALT, AST and GGT and Bilirubin.

Across Phase 3 studies, mean reductions (~3-10%) from baseline in ALT, AST and GGT were observed relative to placebo or to active comparator. The applicant attributes this to weight loss. In contrast, mean increases in bilirubin of similar magnitude were seen in the placebo-controlled dataset (DS-1).

Hypersensitivity and Cutaneous Drug Reactions

Dr. Kwon identified hypersensitivity and cutaneous drug reactions as a risk associated with canagliflozin use. I agree with her assessment. Overall, this risk does not outweigh the benefit of canagliflozin therapy. However, these reactions should be described in the warnings and precautions section of the label with a recommendation to discontinue canagliflozin therapy in patients who develop these events.

Dr. Kwon noted a 4 to 0 imbalance for canagliflozin versus comparators in incident serious adverse events of 'urticaria'. Narratives for these cases are summarized on page 127 of her review. A canagliflozin associated causality is almost certain for two of the four cases (**Case ID#501186** and **Case ID (b) (4)**) as these occurred within hours to days of canagliflozin initiation, improved with dechallenge and were not associated with a reasonable alternative etiology. Generalized urticaria involving the trunk or both the trunk and upper and lower extremities was the basis for categorizing these as serious (one case was treated in hospital for 24 hours). The term 'oozing' is used as a descriptor for **Case ID#501186** but the narrative does not suggest pustulosis, generalized erythema or desquamation. The drug was withdrawn and symptoms improved with withdrawal and treatment with corticosteroids and anti-histamine within hours to days. Systemic symptoms, vital sign changes and or involvement of the face or mucosal surfaces are not noted in the narrative.

A delayed latency (i.e., > 6 months) and temporal association with tramadol initiation makes a canagliflozin related causality less likely for **Case ID#900799**. A delayed

latency (i.e., > 6 months), a past history of urticaria not otherwise specified and improvement despite continued drug therapy makes a canagliflozin related causality unlikely for **Case ID#501382**.

Discontinuations due to hypersensitivity or skin related adverse events were at least twice as frequent in individuals randomized to canagliflozin in the DS-4 dataset. This is shown in Table 40 of Dr. Kwon's review copied below for convenience. Dr. Kwon has also summarized several of these narratives which are found on Pages 131-133 or her review. In most of the described cases a canagliflozin related causality is very likely. In the majority of cases a strong temporal association with initiation of canagliflozin therapy is seen (i.e., some developing the event within hours of starting therapy and most within the first 30 days of therapy), resolution of the rash with drug withdrawal is characteristics and re-challenge is evident in one case (**Case ID#** (b) (4)).

Hypersensitivity-Case ID#s (b) (4): The three discontinuations due to hypersensitivity events describe erythematous, pruritic skin eruptions either: generalized, involving the face only or involving the perineal and lower extremities. Resolution of the adverse drug reactions occurred within days: after drug cessation alone, drug cessation and anti-histamine therapy or drug-cessation and topical anti-fungal and steroids. Mucosal involvement or vital sign instability did not characterize any of these cases.

Angioedema-Case ID#500284: This case describes a 67 year old woman who developed angioedema of the upper lip on Day 22 after initiation canagliflozin. The patient was treated with fexofenadine and dexamethasone and angioedema resolved in 24 hours. No etiology other than canagliflozin is invoked as a possible etiology.

Rash pustular Case ID#900232: This case describes a 48 year old woman with a dermatological history significant for acanthosis nigricans and dry skin who developed a diffuse pustular eruption associated with itching, burning, and tingling and involving the face, trunk, arms and legs on Day 32 after initiating canagliflozin.

Reviewer Comment: *The features of the two later cases which include mucosal swelling and a painful pustular skin eruptions signal more severe types of hypersensitivity reactions. I agree with Dr. Kwon that this adverse reaction should be detailed in the warning and precaution section of the label.*

Table 40: Immune System and Skin and Subcutaneous Tissue Disorders SOC Leading to Discontinuations - DS4

Adverse Event	Cana 100 (N=3092)	Cana 300 (N=3085)	Non-Cana (N=3262)
Immune system disorders SOC	2 (0.1)	1 (<0.1)	0
Drug hypersensitivity	1	0	0
Hypersensitivity	1	1	0
Skin and subcutaneous tissue disorders SOC	12 (0.4)	13 (0.4)	7 (0.2)
Angioedema	1	0	1
Blister	0	0	1
Dermatitis allergic	0	1	1
Dermatitis contact	1	0	0
Eczema	0	1	0
Erythema	0	1	0
Intertrigo	1	0	0
Pemphigoid	1	0	0
Photodermatosis	0	1	0
Photosensitivity reaction	1	0	0
Pruritus	2	2	0
Rash	1	3	1
Rash erythematous	0	2	0
Rash maculo-papular	1	0	0
Rash papular	0	0	1
Rash pruritic	1	1	0
Skin ulcer	0	0	1
Urticaria	2	1	1

Source: ADAE

Hypovolemia Related Adverse Events:

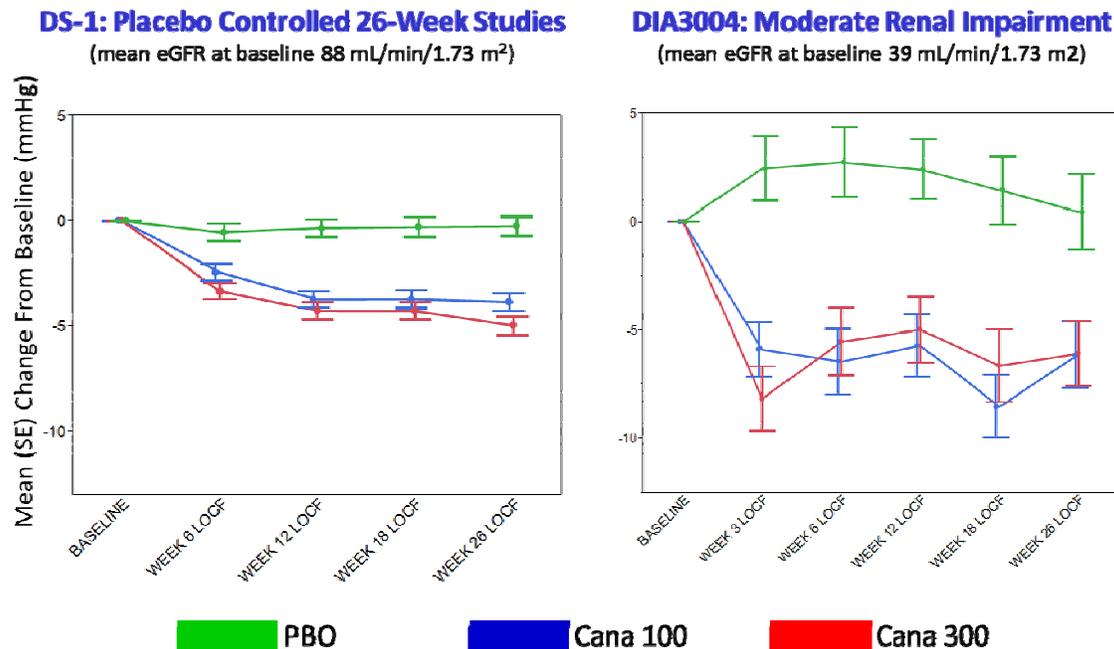
Inhibition of proximal tubular glucose reabsorption by canagliflozin induces an osmotic diuresis. In Trial DIA1007, the applicant showed that canagliflozin results in a transient, immediate (~i.e., within the first 24 hours), dose-dependent increase in urine volume (~200-1100 mL depending on dose) and urinary sodium excretion. These changes last for ~24-48 hours. The transient effect despite continued dosing is attributed to renal adaptation. Indeed in Trial DIA1007, the applicant showed that after 27 days of treatment the amount of filtered sodium excreted in urine had returned to baseline levels.

The changes were associated with immediate (seen on Day 1), dose dependent, persistent decreases in systolic (~4-6 mmHg) and diastolic blood pressure attributed to volume contraction.

In the Phase 3 trials a trend toward slightly larger mean decreases in blood pressure was observed in older individuals, individuals with impaired renal function at baseline and individuals with more advanced diabetes (i.e., DIA3010, DIA3004 and insulin sub-study 3008). Adaption to volume changes in these subpopulations are expected to be

compromised due to greater use of anti-hypertensive agents and/or more advanced disease (e.g., autonomic neuropathy; renal disease; vascular disease).

Figure 10: Baseline Renal Function and Systolic Blood Pressure Changes mITT LOCF population (Jan 10th 2013 EMDAC AC presentation)



To look for adverse events related to volume contraction the applicant queried their safety datasets for adverse events coded to the following MedDRA preferred terms: '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'.

In the DS-3 safety dataset subjects on canagliflozin were ~ twice as likely to experience at least one hypovolemia related event (2.8% versus 1.5% for canagliflozin versus comparators; refer to Table 46 in Dr. Kwon's review). The most frequently reported hypovolemia preferred terms in decreasing order were: 'hypotension', 'dizziness postural', 'orthostatic hypotension' and 'syncope'.

Dr. Kwon shows that the risk of hypovolemia was dependent on baseline disease characteristics of the population studied. In a population of relatively young subjects with an eGFR in the normal range and few comorbid conditions (i.e., DS-1 pooled population) 24, 26 and 28 patients per 1000 patient year of exposure experienced at least one hypovolemia event (~i.e., 1.1-1.2 times more likely than comparator)

In subjects with an eGFR < 60 mL/min/1.73 m² at baseline (i.e., DS-2) and in subjects with established cardiovascular disease at baseline (DIA3008) use of canagliflozin

was associated with a dose dependent increase in the risk of hypovolemia (~1.5 to 3.0 times more likely than comparator).

- In the renal impaired population (i.e., DS-2) 38, 70 and 119 patients experienced at least one hypovolemia related event per 1000 patient-years of exposure to comparator, canagliflozin 100 mg and canagliflozin 300 mg respectively (Refer to Table 45 in Dr. Kwon's review).
- At the interim analysis timepoint for DIA3008, 20, 30 and 50 diabetic subjects with established cardiovascular disease had experienced at least one hypovolemia-related event per 1000 patient-year of exposure to placebo, canagliflozin 100 mg and canagliflozin 300 mg (refer to Table 51 in Dr. Kwon's review).

Subjects randomized to the 300 mg dose experienced their first event at an earlier timepoint than those randomized to the 100 mg dose.

The adverse events themselves were not associated with serious outcomes such as hospitalization and or death nor did they result in a large proportion of subjects discontinuing therapy.

Reviewer comment: *Orthostatic hypotension per se would not be expected to lead to hospitalization. A traumatic event in an elderly caused by a fall due to postural dizziness could lead to hospitalization but this may not be captured as a hypovolemia-related adverse event. We explored the impact of falls on the potential upper extremity fracture risk signal (refer to section below).*

In Table 47 Dr. Kwon shows that hypovolemic adverse events triggered changes to blood pressure, loop diuretic and non-loop diuretic medications 60 days following the event.

In univariate subgroup analyses of the DS-3 dataset the applicant demonstrated that subjects with low baseline eGFR (i.e., <60 mL/min/1.73 m²), male sex, advanced age, use of loop diuretic, use of ACE/ARB in combination with diuretics, low baseline systolic blood pressure ≤110 mmHg and duration of diabetes > 10 were particularly susceptible to these events (refer to Table 49 in Dr. Kwon's review).

Decreased Renal Function and Renal Adverse Events:

This topic has been reviewed in details by Drs. Thompson and Kwon. Refer to their reviews.

Canagliflozin use is associated with a rise in both serum creatinine and blood urea nitrogen (BUN). These changes likely result from decreased renal perfusion secondary to mild volume contraction. The observed blood pressure reduction and decreases in albumin to creatinine ratio in the canagliflozin versus placebo are consistent with a hemodynamic drug effect.

Mean serum creatinine (sCr) changes (mITT LOCF population):

Changes in serum creatinine were seen in the Phase 3 trials. The magnitude of the changes was dose, time and population dependent.

In the pool of subjects with normal to mildly impaired renal function (DS-1; mean baseline creatinine 0.9 mg/dL) the maximum rise in sCr occurred at the earliest ascertained time point (i.e., Week 6) and was dose dependent. The mean rise in serum creatinine at Week 6 was 0.01, 0.03 and 0.05 mg/dL for the placebo, canagliflozin 100 and 300 mg doses, respectively (i.e., representing a 3 to 5% mean increase from baseline at peak for the 100 and 300 mg canagliflozin dose respectively). Early mean changes in creatinine returned toward baseline levels after Week 6 but creatinine never reaches baseline levels. At Week 26 (i.e., end of treatment) creatinine was 0.00, 0.02 and 0.03 mg/dL above baseline in the placebo canagliflozin 100 and canagliflozin 300 dose groups, respectively.

In subjects with moderate renal dysfunction (DIA3004; mean baseline creatinine 1.6 mg/dL) the maximum rise in serum creatinine also occurred at the earliest ascertained time point (i.e., Week 3) and was dose dependent. The mean rise in serum creatinine at Week 3 was 0.03 mg/dL, 0.18 and 0.27 mg/dL for the placebo, canagliflozin 100 and 300 mg, respectively (i.e., representing a 13% and 19% mean increase from baseline at peak for the 100 and 300 mg dose respectively). Early changes in creatinine returned towards baseline after Week 3 but creatinine never returned to baseline levels. At Week 26 (i.e., end of treatment) creatinine was 0.02, 0.13 and 0.18 mg/dL above baseline in the placebo, canagliflozin 100 and canagliflozin 300 dose groups respectively.

A rise in blood urea nitrogen which persisted throughout the trial was also seen and suggests the rise in serum creatinine is due to decreased glomerular filtration as opposed to interference with tubular secretion of creatinine.

Reviewer Comment: *Even though the absolute mean changes in serum creatinine are small small changes could impact diabetic therapy. For example, a subject with moderate renal function on metformin who has a small deterioration in renal function with canagliflozin therapy may no longer be a candidate for metformin. In the add-on to metformin trials in subjects with normal to mildly impaired renal function at baseline more subjects randomized to canagliflozin withdrew on the basis of creatinine or eGFR changes which made them no longer eligible for metformin (See Table 41 in Dr. Kwon's review). The label should inform prescribers about potential renal function changes with canagliflozin, highlight the population at most risk of this event and recommend routine monitoring of renal function when initiating therapy.*

Changes to renal function estimated using the four variables (i.e., creatinine, age, sex and race) modified diet in renal disease equation (i.e., MDRD) paralleled changes to creatinine. At end of trial (Week 26) the mean eGFR was 0.5, 1.8 and 3.0% lower for subjects randomized to placebo, canagliflozin 100 and canagliflozin 300 in DS-1

(mean baseline eGFR 88 mL/min/1.73 m²). In contrast mean eGFR decline at peak and at end of treatment was larger in subjects with moderate renal dysfunction at baseline in DIA3004 (mean baseline eGFR 39 mL/min/1.73 m²). In these patients mean eGFR had declined by 2, 8 and 9% for placebo, canagliflozin 100 and canagliflozin 300 mg respectively at end of trial (Week 26). Changes to eGFR over time are shown in figures 19 and 20 of Dr. Kwon's review.

Reversibility of eGFR changes:

Although figures 19 and 20 in Dr. Kwon's review suggest a partial return of renal function towards baseline after Week 6 and Week 3 respectively, at end of treatment renal function in the canagliflozin group remained significantly worse than renal function in the placebo group. The applicant did not routinely measure post-treatment eGFR to ascertain whether eGFR differences between canagliflozin and placebo seen at end of treatment disappear after an adequate washout period (i.e., suggesting full reversibility after correction of volume depletion).

Reviewer Comment: *I agree with Dr. Thompson that reversibility should be evaluated in the post-marketing setting. Canagliflozin mediated volume changes could predispose susceptible patients to repeat episodes of acute kidney injury which could have an adverse effect on renal function over time. Since loss of renal function is an issue in the diabetic patient population due to underlying diabetic nephropathy, I agree that this is an issue worth pursuing. I propose the applicant be asked to demonstrate reversibility of the eGFR function changes in individuals at risk of hemodynamically mediated kidney injury (i.e., subjects participating in the cardiovascular outcomes trial). The goal would be to demonstrate that the change from baseline in eGFR between placebo and canagliflozin are similar after a washout period.*

Peak and mean eGFR changes according to impaired renal function strata:

No noticeable 'absolute' differences in peak or end of trial change from baseline in renal function were noted between subjects with a baseline eGFR between 30 to less than 45 mL/min/1.73 m² and those with a baseline eGFR \geq 45 but below 60 mL/min/1.73 m² in the renal impairment dataset. However, the percent loss in renal function is greater in patients with lower renal functional reserve. The two frequency distribution figures show the proportion of subjects (Y-axis) according to eGFR changes from baseline to end of treatment in 1 mL/min/1.73 m² increments (X-axis) (Source: response to information request received 12/12/2012). The tables immediately below the figures show the mean, median and range of eGFR change in the two subgroups.

Figure 5.3.3: Frequency Distribution of Last eGFR Changes for canagliflozin pool versus placebo
ISS DS2 – Subjects with baseline eGFR of 45 to <60 mL/min/1.73 m²

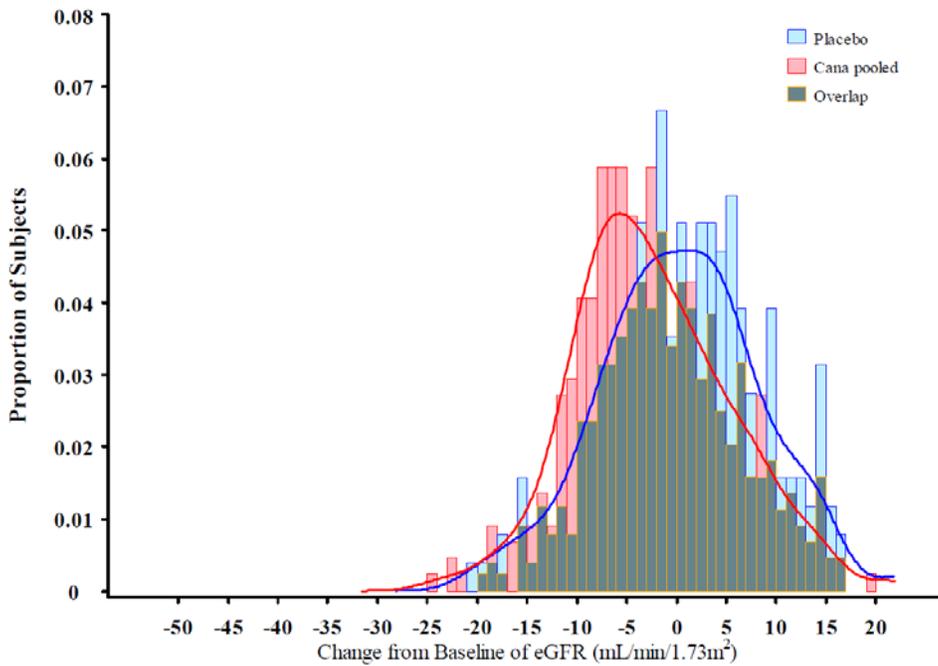


Table 5_3: Descriptive Summary of eGFR(mL/min/1.73m²)(mITT, Regardless of Rescue Within 2 Days of Last Dose of Study Drug)
 (ISS dataset 2 - Baseline eGFR (45-<60): Modified Intent-To-Treat Analysis Set)

	Placebo (N=255)	Cana 100 mg (N=213)	Cana 300 mg (N=230)	All Cana (N=443)
Change from Baseline at Endpoint				
N	255	213	230	443
Mean (SD)	0.69 (8.722)	-1.24 (9.035)	-2.61 (8.790)	-1.95 (8.924)
Median	0.00	-2.00	-4.00	-3.00
Range	(-21;39.0)	(-25;41.0)	(-23;42.0)	(-25;42.0)

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Figure 4.3.3: Frequency Distribution of Last eGFR Changes for canagliflozin pool versus placebo

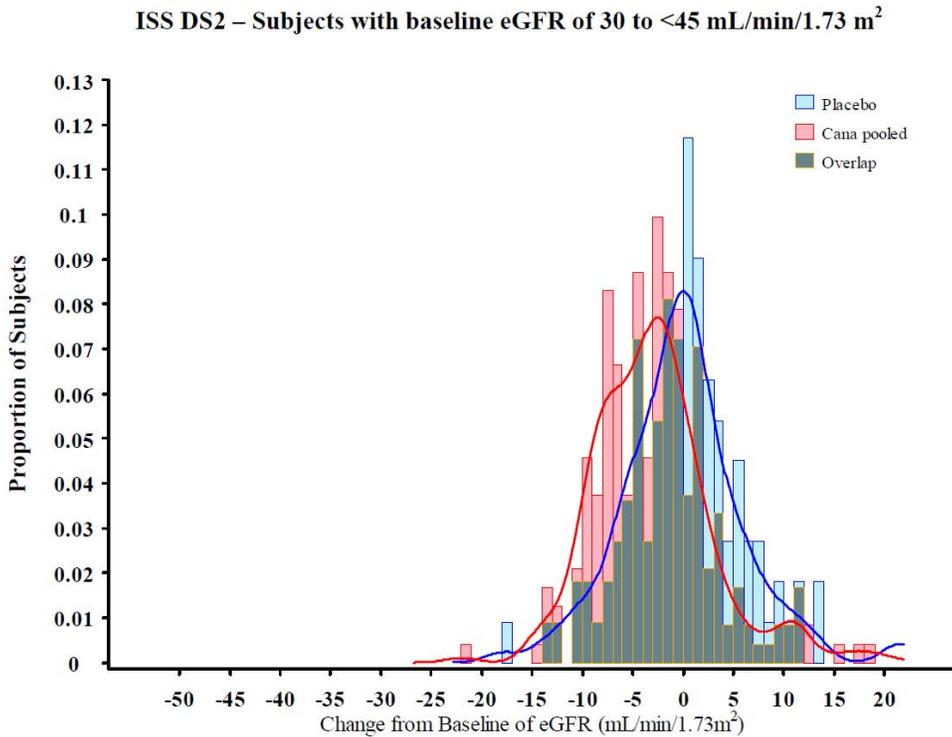


Table 4_3: Descriptive Summary of eGFR(mL/min/1.73m²)(mITT, Regardless of Rescue Within 2 Days of Last Dose of Study Drug)

(ISS dataset 2 - Baseline eGFR (30-<45): Modified Intent-To-Treat Analysis Set)

	Placebo (N=112)	Cana 100 mg (N=119)	Cana 300 mg (N=122)	All Cana (N=241)
Change from Baseline at Endpoint				
N	112	119	122	241
Mean (SD)	0.25 (7.073)	-2.63 (6.412)	-2.52 (7.203)	-2.57 (6.810)
Median	0.00	-3.00	-3.00	-3.00
Range	(-18;35.0)	(-22;28.0)	(-15;26.0)	(-22;28.0)

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Proportion of Patients with Significant eGFR Declines:

The applicant performed several pre-defined limit of change analyses (summarized in Table 53 of Dr. Kwon’s review). These analyses demonstrated that subjects with moderate renal impairment at baseline were more likely to experience at least one episode of significant renal function decline during the trial time period (26-weeks) compared to subjects randomized to placebo. In DS-2 (mean baseline eGFR 48 mL/min/1.73 m²), 4.9%, 9.3% and 12% of subjects randomized to placebo, canagliflozin 100 and 300 mg experienced at least one episode of eGFR decline of 50% or greater at any time during the trial. However, the proportions of individuals showing significant decline in eGFR from baseline at the last treatment visit were similar between the comparator and two canagliflozin groups.

Renal-related Adverse Events:

To evaluate renal adverse event incidence across the canagliflozin trials the applicant queried the various safety databases for events coded to the MedDRA preferred terms 'blood creatinine increased', 'glomerular filtration rate decreased' and for events coded to any of the preferred terms included in the 'acute renal failure' Standardized MedDRA Query (refer to Page 156 of Dr. Kwon's review for the list of preferred terms included in this query).

These analyses showed that canagliflozin was associated with a dose dependent increase in occurrence of renal related adverse events. In subjects with mild to moderate renal function at baseline no risk increase was seen between placebo and the 100 mg dose of canagliflozin but a 3-fold risk increase between placebo and the 300 mg dose was seen (14 versus 36 patients per 100 patient year of exposure). Subjects with moderate renal impairment at baseline (i.e., DS-2) had a higher baseline risk and were > 2 times as likely to experience at least one renal related adverse event if they were randomized to either canagliflozin dose groups compared to placebo (54 versus ~126 patients per patient year of exposure).

These events led to discontinuations in > 50% of cases in the mild to moderate renal impaired population (probably due to metformin eligibility criteria) but were not serious. In the moderate renal impairment population most of the events did not lead to discontinuations and did not meet the regulatory definition of a serious event.

Population at Risk of Renal Adverse Events Associated with Canagliflozin Use:

Baseline variables associated with the greatest absolute risk increase for renal adverse events were; renal impairment at baseline (those with an eGFR < 60 mL/min being particularly susceptible), use of loop diuretics, use of ACEi and/or ARB and use of loop diuretic in combination with ACEi and/or ARB.

Causality Assessment for Significant Renal Adverse Events:

A clinical endpoint committee was asked to blindly adjudicate the potential causal relationship between drug and the following significant renal adverse events

- Sustained doubling of serum creatinine from baseline value (or $\geq 50\%$ decrease in eGFR from baseline) while receiving study drug. "Sustained" was defined as a repeat value occurring ≥ 4 weeks after the initial finding with the subject remaining on study drug
- Doubling in baseline serum creatinine (or $\geq 50\%$ decrease in baseline eGFR) at last recorded laboratory value.
- End stage renal disease (ESRD, new or worsening) or renal replacement (dialysis or transplant).

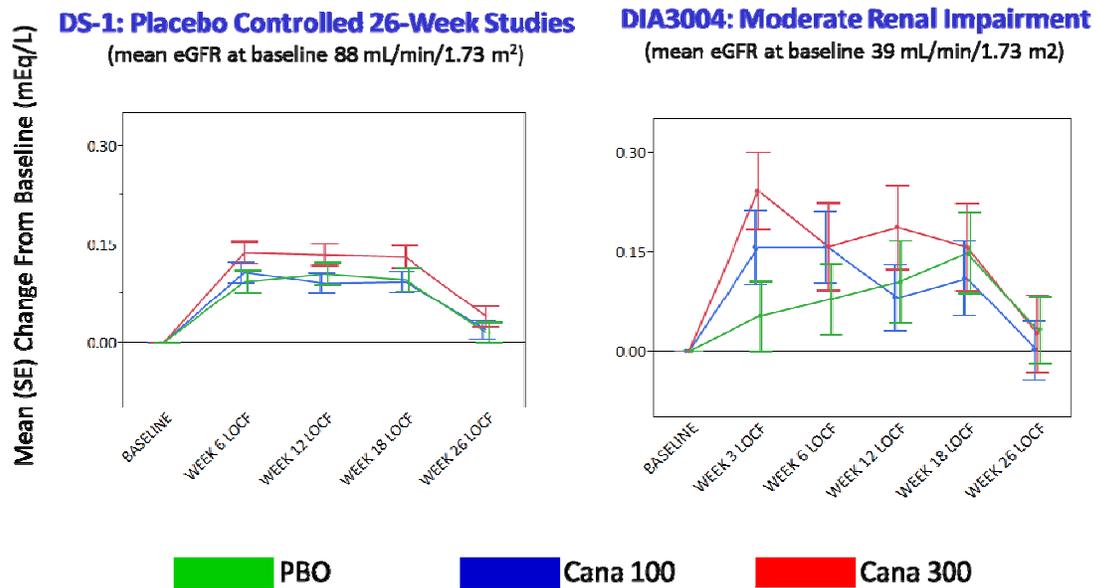
As of the 4 Month Safety Update, 43 events met adjudication criteria. These events occurred in 0.41%, 0.39% and 0.46% of subjects randomized to comparators,

canagliflozin 100 and canagliflozin 300. No clear difference in adjudicated causation is seen. Dr. Kwon reviewed a sample of narratives and agreed with causality assessment in this sample.

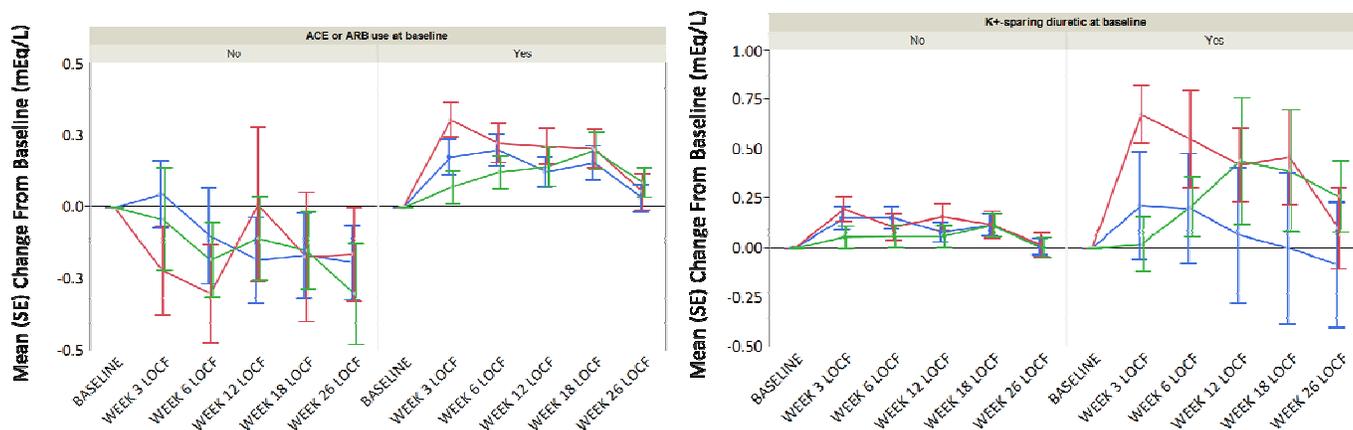
Hyperkalemia:

Serum Potassium Changes Central Tendency Analyses:

Mean increases in serum potassium from baseline were seen. The magnitude of the observed change was dependent on time, dose and baseline population characteristic. The figure (source: reviewer's own analysis of ADLCM12.xpt dataset) summarizes the mean changes from baseline over time in the mITT population with normal renal function or moderate impairment at baseline (DS-1) and in subjects with moderate renal impairment at baseline (DIA3004).



Serum potassium increases were greatest early after initiation of canagliflozin and in subjects receiving concomitant medications which block the renin-angiotensin-aldosterone axis as illustrated in the figures showing mean serum potassium changes by subgroup of co-administered ACE/ARB yes/no on the left and co-administered potassium sparing diuretic yes/no on the right in DIA3004 below (note: mean baseline potassium in all groups was ~ 4.6-4.7 mEq/L and upper normal range was 5.4 mEq/L).



As shown in the figures and in Table 98 of Dr. Kwon's review mean serum potassium changes returned to baseline by trial end.

Reviewer Comment: *The large mean changes in serum potassium occurring early in patients with moderate renal impairment and on potassium sparing diuretic randomized to the 300 mg dose of canagliflozin are worth noting (i.e., at Week 3 the average potassium value in the high dose group was ~ at the upper limit of the normal range). To reduce the risk of hyperkalemia prescribers should be warned that high blood potassium can occur in specific settings so that they can adequately monitor for and treat this event should it occur. Renin blocking agent, ACEi, ARB and potassium sparing diuretics are widely used in patients with diabetes to treat highly prevalent co-morbid conditions such as nephropathy, hypertension, and heart failure. Co-morbid conditions related to progression of diabetic kidney disease (i.e., decrease renal function and type IV renal tubular acidosis) would also be expected to place patients at increased risk.*

Proportion of patients experiencing potassium increases above the upper normal limit and > 15% above baseline value

In the subjects with normal renal function or mild renal impairment (i.e., DS-1), the proportion of subjects with at least one episode of serum potassium outside the upper normal range and > 15% above the baseline value was greater in the 300 mg dose group (7.0%) than in the placebo group (4.8%). A similar observation was made in subjects with impaired renal function at baseline (i.e., DS-2) (12.0% versus 7.9% for canagliflozin versus placebo). The proportion of patients randomized to 100 mg per day and experiencing significant potassium changes was similar to placebo in both groups.

Hyperkalemia Related Adverse Events

Adverse events coded the preferred terms 'Hyperkalemia' and 'Blood potassium increased' occurred slightly more frequently in subjects randomized to canagliflozin in all datasets (refer to Table 100 of Dr. Kwon's review). An imbalance in adverse events considered 'serious' (3 versus 0) was seen in the datasets of subjects with moderate renal impairment (i.e., DS-2) and in the largest dataset (i.e., DS-3).

Tachycardia Related Adverse Events

To evaluate the impact of hyperkalemia on cardiac excitability we examined adverse events data in DS-3 for tachycardia related adverse events by pooling all tachycardia related preferred terms reported. The following preferred terms were included in the pool; 'Atrial fibrillation', 'Tachycardia', 'Sinus tachycardia', 'Atrial flutter', 'Supraventricular tachycardia', 'Ventricular fibrillation', 'Cardiac flutter', 'Tachycardia paroxysmal' and 'Ventricular tachycardia'. No imbalance in the incidence of tachycardia related events was evident from this search [1.0% (32/3262) versus 0.9% (56/6177) for placebo versus canagliflozin].

Finally, it is worth noting that in the overall population and in the population of patients participating in the dedicated cardiovascular outcomes trial no imbalances in cardiovascular death were seen (refer to cardiovascular safety section below).

Venous thromboembolic events:

Per request of the Agency, the applicant followed venous thromboembolic events as events of special interest in the Phase 3 program. Canagliflozin use is associated with intravascular volume depletion and predisposes to hemoconcentration. These changes could, in theory, predispose to venous thromboembolic events (i.e., VTEs). The applicant acknowledges this theoretical possibility by pointing to the precautions section of the furosemide label which states;

- *“Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possible vascular thrombosis and embolism, particularly in elderly patients.”*

The applicant also correctly points out that in large cardiovascular trials employing other diuretics (e.g., ALLHAT and ADVANCE trials) an increase in VTE events was not observed.

A prospective plan to identify VTE events was implemented. This included investigator querying participants for these events and documenting this on the electronic case report form (eCRF) as well as regular monitoring of the safety database for reported adverse event terms coded to the Standard MedDRA Query (SMQ) 'embolic and thrombotic events, venous'. Events were prospectively adjudicated by a blinded, independent, endpoint adjudication committee composed of three subject matter experts using a standard set of definitions (refer to EAC charter Appendix 5 of ISS).

A total of 18 treatment emergent events were confirmed to be VTEs at the time of NDA submission in DS-4. Two additional cases were reported at the 4 Month Safety Update (1 case each on canagliflozin 100 mg and comparators).

Table 59 in Dr. Kwon's review summarizes the findings for VTE events in DS-4. The risk of 'any' (n=5 events) and 'serious' (n=4 events) VTE events for canagliflozin 100

mg was identical to that of comparator (1.5 events per 1000 patient year of exposure). The risk of 'any' (n=8 events) and 'serious' VTE (n=8 events) in canagliflozin 300 mg was increased (2.4 events per 1000 patient year of exposure). The risk increase was driven by three excess cases in the 300 mg dose group. The majority of events in all three groups were coded to the preferred terms 'deep vein thrombosis' and 'pulmonary embolism'.

In 7 out of 18 cases (i.e., 2, 2, and 3 on canagliflozin 100 mg, 300 mg and comparator respectively), risk factors other than drug were identified as a possible contributor to the event (i.e., immobilization due to hospitalization for illness or fracture; orthopedic or gynecological surgery). The median time to first embolic event tended to occur earlier on canagliflozin 300 mg. This was driven by two pulmonary embolism cases which occurred on Day 5 (**Case ID#** (b) (4)) and Day 16 (**Case ID#** (b) (4)) after randomization. Only 1/18 cases (**Case ID#200184** Cana 300 mg) had a volume depletion related adverse event noted approximately 3 months before thrombotic event occurrence.

Overall it does not appear that canagliflozin greatly increases the risk of venous thromboembolic events over baseline risk in this population⁴. The imbalance in risk for the 300 mg dose was driven by three excess events and could represent a chance finding. This seems to be supported by the fact that the risk difference between the 300 mg and the two other randomized groups (100 mg and comparator) decreased with the addition cases reported at the 4 Month Safety Update (1 case each in the 100 mg canagliflozin dose group and comparator group). However given the dose-dependency and the temporal association between drug initiation in two cases; I suggest these events continue to be followed as events of special interest in the dedicated cardiovascular outcomes trial.

Cardiovascular Safety

This topic is reviewed in details by Drs. Andraca-Carrera and Kwon.

Diabetes Guidance: Pre-Market Cardiovascular Risk Assessment.

To assess cardiovascular risk associated with use of canagliflozin the applicant relies on a pre-specified meta-analysis of nine clinical trials. The nine trials include one Phase 2 trial (i.e., DIA2001), seven Phase 3 trials primarily designed to demonstrate glycemic efficacy (i.e., DIA3002, DIA3004, DIA3005, DIA3006, DIA3009, DIA3010 and DIA3012) and one dedicated cardiovascular outcomes trial (i.e., DIA3008 or "CANVAS").

⁴ Tsai AW (2002), Cushman M, Rosamond WD, et al. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Archives of Internal Medicine 2002; 162:1182-9.

Petrauskiene V (2005), Falk M, Waernbaum I, Norberg M, Eriksson JW. The risk of venous thromboembolism is markedly elevated in patients with diabetes. Diabetologia 2005;48(5):1017-21.

The primary objective of the pre-specified meta-analysis was to exclude an 80% excess cardiovascular risk based on a primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and hospitalization for unstable angina (i.e., MACE+). The meta-analysis was designed to demonstrate that the upper 95% confidence interval around the hazard ratio for MACE+ between canagliflozin and comparators was below 1.8. The applicant had planned a first analysis after accrual of 160 MACE+ events. The analysis was to be based on a stratified (i.e., CANVAS and non-CANVAS trials) cox-proportional hazards model.

The applicant had also intended to utilize the pooled data to exclude a cardiovascular risk excess of 30% or more (i.e., a hazard ratio exceeding 1.3) either pre or post-marketing. A 30% excess risk would have been considered excluded if the upper bound of the 99.9% confidence interval around the hazard ratio for MACE+ obtained to rule out 1.8 was below 1.3 (i.e., 2-sided $\alpha=0.001$). Two additional analyses for 1.3 were pre-specified: one after accrual of 500 MACE+ events and another after 700 MACE+ events in case a 30% excess cardiovascular risk could not be rejected at 500 events.

In the entire program cardiovascular events were identified prospectively and adjudicated blindly using a set of standard definitions by an independent cardiovascular endpoint committee. All events adjudicated before the data cutoff date of January 31, 2012 were included in the analysis submitted to the NDA. The treatment emergent time period was defined as the time of randomization to 30 days after the last dose of randomized treatment. Subjects were censored if; they had a primary event, they discontinued the study, or at the end of treatment + 30 days.

Specifics Related to the CANVAS Trial Design

Here I review key differences between CANVAS and other Phase 3 trials.

CANVAS was an adaptively designed, randomized, double-blind, placebo-controlled, 3 parallel group, multinational, multicenter trial. Randomization was 1:1:1 to one of two canagliflozin doses or placebo. The aim of the trial was to compare cardiovascular risk between subjects randomized to canagliflozin plus standard of care versus those randomized to placebo plus standard of care.

The sponsor had planned an adaptive or phased recruitment in CANVAS. According to this plan a first cohort of ~4500 subject referred to as 'Cohort A' would initially be recruited. This number was selected based on the numbers of events needed to support the meta-analysis of cardiovascular events across the Phase 2-3 program to exclude the 1.8 risk ratio.

Cohort A was to be followed for ~4 years after which time a CANVAS specific interim analysis to determine the feasibility of demonstrating cardiovascular benefit would be

conducted by an independent data monitoring committee (IDMC). Based on the result of this analysis, the IDMC would or would not recommend that the Steering Committee re-open enrollment. An additional 4500 to 14000 subjects could be randomized in Cohort B if enrollment were to have been re-opened. After noting that canagliflozin use was associated with an increase in mean LDL cholesterol, the sponsor unblinded CANVAS to more fully explore the impact of this change on cardiovascular safety for NDA submission and abandoned the plan to re-open CANVAS enrollment.

CANVAS, in contrast to trials designed primarily for glycemic efficacy, enrolled a population at high risk for future cardiovascular events. In order to be eligible for the CANVAS trials subjects had to either be ≥ 30 years old and have a documented history of symptomatic cardiovascular disease or be ≥ 50 years old and have at least two established risk factors for cardiovascular disease. At full enrollment 70% of the patients were to have had a history of symptomatic cardiovascular disease and 30 % to have had at least two cardiovascular disease risk factors.

A documented history of symptomatic cardiovascular disease was defined as any history (> 3 months prior to screening) of the following:

- Stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease.

Risk factors for cardiovascular disease were to be present at screening and were:

- Duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria (see Section 3.2, Study Design Rationale, for definition), or documented HDL-C of <1 mmol/L (<39 mg/dL).

Patients with: poor diabetes control at baseline, with a history of severe hypoglycemic episode, with recent cardiovascular events (i.e., < 3 months), with findings on 12-lead EKG were excluded from participation.

Subjects not on metformin who had a screening estimated glomerular filtration rate (eGFR) below 30 mL/min/ 1.73m^2 were excluded. Male subjects on metformin at screening were excluded if they had a serum creatinine ≥ 1.4 mg/dL and women subjects on metformin were excluded if they had a serum creatinine ≥ 1.3 mg/dL.

The first Cohort A subject was enrolled in November 2009 and the last Cohort A subject was randomized in March 2011 (i.e., by the NDA data cutoff date CANVAS

was fully enrolled). 4330 subjects were randomized to placebo (n=1442), canagliflozin 100 mg (n=1445) and canagliflozin 300 mg (n=1443).

Results: Meta-analysis of Cardiovascular Safety

In light of design differences between CANVAS and non-CANVAS trials, heterogeneity in the pool of subjects used for the meta-analysis was expected. Dr. Andraca-Carrera summarizes main differences in baseline characteristics between the pooled population derived from the 8 Phase 2-3 studies and the population enrolled in CANVAS in Tables 4-6 of his review. Subjects in CANVAS were older and majority males (~70%). They were more likely to: be current smokers (18 versus 12%), have an eGFR below 60 mL/min/1.73 m² (17 versus 10%), have established cardiovascular disease (57 versus 32%), use a statin drug (72 versus 57%), have a systolic blood pressure greater than 140 mmHg (55 versus 38%), and have had diabetes for 10 years or longer (70 versus 49%).

Dr. Andraca-Carrera noted no discernible differences in follow-up times between canagliflozin and placebo groups in either CANVAS trial participants or in the pool of non-CANVAS trial participants. Reasons for discontinuation across the 9 trials were also similar.

The meta-analysis of cardiovascular safety was based on 201 MACE+ events. 161 events (~80%) occurred in CANVAS. The number of events contributed by each of the nine trials for each treatment arm is shown in Table 11 of Dr. Andraca-Carrera's review.

In the mITT population 130 (18.9 cases per 1000 PYE) subjects randomized to canagliflozin had at least one adjudicated MACE+ event versus 71 on comparators (20.5 cases per 1000 PYE). The hazard ratio (95% CI) for MACE+ derived from the cox-proportional hazards model was 0.91 (0.68, 1.21). This analysis excludes a relative cardiovascular risk increase of 80% or greater based on the upper bound of the 95% CI being below a hazard ratio of 1.8. A secondary analysis using MACE alone (i.e., excluding the component 'hospitalization for unstable angina' from the composite primary endpoint) was consistent with the primary analysis. These results are shown below.

Table 13: Primary (MACE+) and secondary analysis (MACE) in Pool of 9 Trials (Source: adapted from Table 13 in Dr. Andraca-Carrera's review)

	Canagliflozin N= 6396 PY = 6876	Comparators N = 3327 PY = 3470	Hazard Ratio (95% CI)
MACE+ (rate per 1000 PYE)	130 (18.9)	71 (20.5)	0.91 (0.68, 1.21)
MACE (rate per 1000 PYE)	104 (15.1)	53 (15.3)	0.98 (0.70, 1.36)

Dr. Andraca-Carrera performed several subgroup analyses to assess the impact of dose, sex, race, age, country of randomization, baseline BMI, baseline history of

cardiovascular disease, baseline use of statin drugs and baseline eGFR on cardiovascular risk using MACE+ (refer to Table 20-27 in his review). Results across subgroups were generally consistent with results for the overall population.

Another secondary analysis was carried out on each of the individual components of the MACE+ primary endpoint. In this analysis three of the four components had a point estimate below a hazard ratio of 1 and one component had a point estimate above one (stroke). The uncertainty around the estimate of risk for each of the four MACE+ components was large and crossed unity. This analysis was consistent with the primary analysis and does not allow one to conclude that a risk difference exists between groups for any of the individual components.

Table 14: Secondary Analysis Individual Components (Source: Table 14 in Dr. Andraca-Carrera's Review)

	Canagliflozin N=6396	Comparators N=3327	Hazard Ratio (95% CI)
CV-Death	21	16	0.65 (0.34, 1.24)
MI	45	27	0.83 (0.51, 1.34)
Stroke	47	16	1.46 (0.83, 2.58)
Hospitalization for UA	26	18	0.65 (0.39, 1.30)

As shown above, the only component with a point estimate above unity was fatal/non-fatal stroke. 79 and 56% of all strokes in canagliflozin and placebo respectively were adjudicated as ischemic in origin. The imbalance was driven by an excess of 'non-fatal' strokes in the pool of non-CANVAS trial [i.e., 2.6 strokes per 1000 PYE (n=9 incident events) versus 0.6 strokes per 1000 PYE (n=1 incident event) for canagliflozin and comparator respectively] and in the first 30-days of CANVAS (4 vs. 1 vs. 0 incident events in the canagliflozin 100 mg vs. 300 mg vs. placebo groups). As shown in Table 18 of Dr. Andraca-Carrera's review, after the first 30-days of CANVAS the risk ratio (95% CI) for strokes was 1.01 (0.55, 1.87).

The applicant performed an ad-hoc stroke analysis per request of the European Medicines Agency and submitted the results of this analysis to the NDA on November 30th 2012. The update was based on the original pool of 9 trials + two additional completed trials, included 82 total fatal/nonfatal stroke events (i.e., 19 additional events) and had a data cutoff date of November 20th 2012. The point estimate for the risk ratio (95% CI) for this ad-hoc analysis was 1.29 (0.80, 2.09). This analysis shows stroke risk diminishing with additional data and supports the notion that the imbalance in the NDA dataset represents a chance finding. Limitations of this analysis are that it was not pre-specified, included a different set of trials than in the pool used for the meta-analysis and was not reviewed by the Agency.

Early CV Events in CANVAS

Examination of the Kaplan-Meier survival plot suggested that the assumption of hazards proportionality for the Cox proportional hazards model could have been violated (i.e., survival curves cross at ~ Day 40 see figure below). Dr. Andraca-

Carrera evaluated hazards proportionality over time using a statistical method (i.e., Schoenfeld residuals method) and showed that hazards proportionality may not have been met.

Figure 4. Estimated Probability and 95% CI of MACE-plus by Time in All Trials
Source: Created by reviewer. Dataset: adttecv.xpt

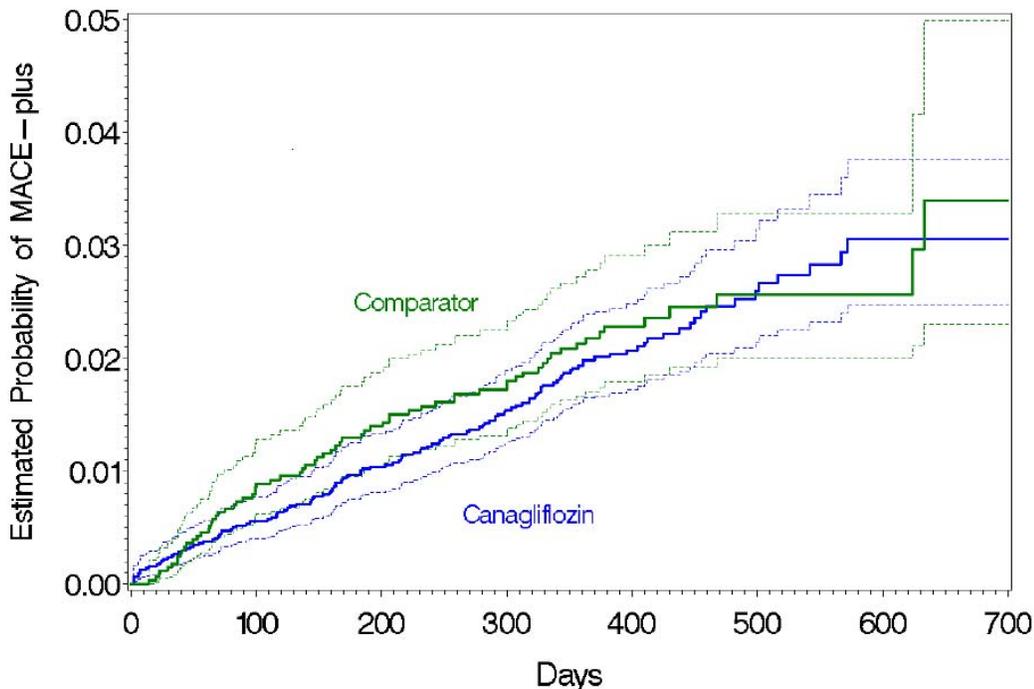


Figure 11 Survival Plot, MACE +, Pool of 9 Trials (Source: Dr. Andraca-Carrera's Review)

Kaplan-Meier survival plots of MACE+ for the CANVAS and non-CANVAS strata showed that violation of the hazards proportionality was caused by an imbalance in early MACE+ events not favoring canagliflozin in CANVAS (refer to figure 5 and 6 of Dr. Andraca-Carrera's review). In the pool of 8 other Phase 2-3 trials (i.e., non-CANVAS stratum) hazards proportionality was met for the entire trial period and no imbalance in early MACE+ events was seen.

Within the first 30 days of CANVAS, 13 MACE+ events occurred in patients randomized to the two canagliflozin dose groups versus 1 event in patients randomized to placebo (~6.5 to 1 imbalance when adjusting for uneven randomization). Seven of these events occurred within seven days of trial initiation, no dose-relatedness is evident and no single component of the composite endpoint predominated. The majority of these events were non-fatal strokes (n=6 and majority ischemic and one fatal) and non-fatal myocardial infarctions (n=5; majority ST-elevation MI 3 vs. 2).

The dose, onset day and type of MACE+ event, baseline hematocrit and serum hemoglobin in these 14 cases are summarized below.

Table 15: Cases Early MACE+ Events CANVAS

Case ID#	Age	Sex	TRT Arm	Onset Day	MACE+ Event	Baseline Hct (%)	Baseline Hg (g/dL)
(b) (4)	79	M	300	2	Stroke	0.44	14.2
	65	M	100	2	UA	NA	16.8
	68	F	100	2	Stroke	0.36	11.6
	57	M	300	6	MI	0.44	14.5
	76	M	300	6	MI	0.36	12.5
	54	F	300	7	CV Death/Stroke	N/A	N/A
	68	M	100	7	Stroke	0.42	13.7
	37	F	300	12	MI	0.44	15
	57	M	100	14	UA	0.44	15
	76	M	100	21	MI	0.39	13
	67	M	PBO	23	MI	0.39	14.4
	61	M	100	24	MI	0.44	15.1
	57	M	100	26	Stroke	0.43	15.3
	56	M	300	29	Stroke	0.53	16.5

Sample size: 2886 canagliflozin and 1441 placebo

In an attempt to identify features that would predict early onset events we explored some of the baseline characteristics for the 13 patients randomized to canagliflozin who had events early and contrasted these to the baseline characteristics of patients on canagliflozin who had events after 30 days and all patients who had events on placebo.

The result of this exploratory analysis is shown below. Cardiovascular risk factors (i.e., male sex, smoking, hypertension, albuminuria, history of myocardial infarction) in the subgroup of patients with early events appeared to be slightly more prevalent at baseline in this subgroup suggesting early events occurred in individuals with higher baseline risk for CV events. This is summarized in table format below (source: sponsor response 12/21/2012 to information requested by the Agency on 12/18/2012).

	Canagliflozin within 30 days (N=13)	Canagliflozin after 30 days (N=95)	Placebo All Subjects with CV event (N=53)
Mean age, years	62.4	63.2	64.4
Male, %	77%	73%	64%
Mean Baseline HbA1c (%)	8.3	8.2	8.2
Mean Baseline eGFR	77.3	75.1	73.5
Mean Baseline LDL-C (mg/dL)	101	100	94
Baseline BMI (kg/m ²)	31	33	33
Previous history of CV, %:	69%	79%	85%
History of HTN	92%	88%	83%
History of MI	54%	44%	45%
History of dyslipidemia	46%	63%	72%
CV Risk Factor, %:			
Current smoker	31%	18%	13%
Diabetes ≥10 years	77%	63%	72%
HDL-C (<39 mg/dL)	31%	33%	42%
Micro or macro-albuminuria	54%	36%	34%
SBP >140 mmHg at Screening	46%	43%	43%

Dr. Kwon also reviewed individual narratives by category of events for each of the thirteen individuals with early events on canagliflozin to assess for the presence of coincident canagliflozin related adverse events (e.g., orthostasis⁵) and explore potential commonality between cases (i.e., co-administered medications). For **Case ID [REDACTED]** (Day 2: ischemic stroke followed by CV-death) and **Case ID [REDACTED]** (non-fatal MI) symptoms consistent with the index events were reportedly present at baseline and prior to initiation of canagliflozin therapy. If these subjects were truly having symptoms prior to baseline it is unclear to me why they were randomized.

In several cases symptomatology (i.e., dizziness) consistent with orthostasis was more likely attributable to the underlying stroke event than to volume changes (i.e., these symptoms were accompanied by coincident visual disturbances and ataxia). **Case ID [REDACTED]** (i.e., non-fatal basal ganglia and parietal periventricular strokes) was the only case where blood pressure at the time of the event was notably lower than at baseline (i.e., 90/60 versus 118/83 mmHg). However, information concerning symptoms and/or vitals before the event is missing from most narrative.

The stroke cases are remarkable for the fact that in 4 out of 6 cases symptoms, constellation (dizziness/vertigo/nausea, ataxia, gait disturbance, visual disturbance, and dysarthria), and stroke location on imaging (i.e., pons, basal ganglia, periventricular white matter) suggest strokes in multiple regions supplied by tributaries of the vertebral and basilar arteries (i.e., deep brain structure and brain stem/cerebellum). Vertebrobasilar strokes typically occur in small vessel tributaries

⁵ Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987-1996. Stroke. 2000; 31(10):2307-2313.

and are most often due to embolic occlusion (note: all 4 subjects were on ASA). In specific cases however vertebrobasilar ischemia has been associated with hemodynamic changes. In a review⁶ of vertebrobasilar disease the authors write:

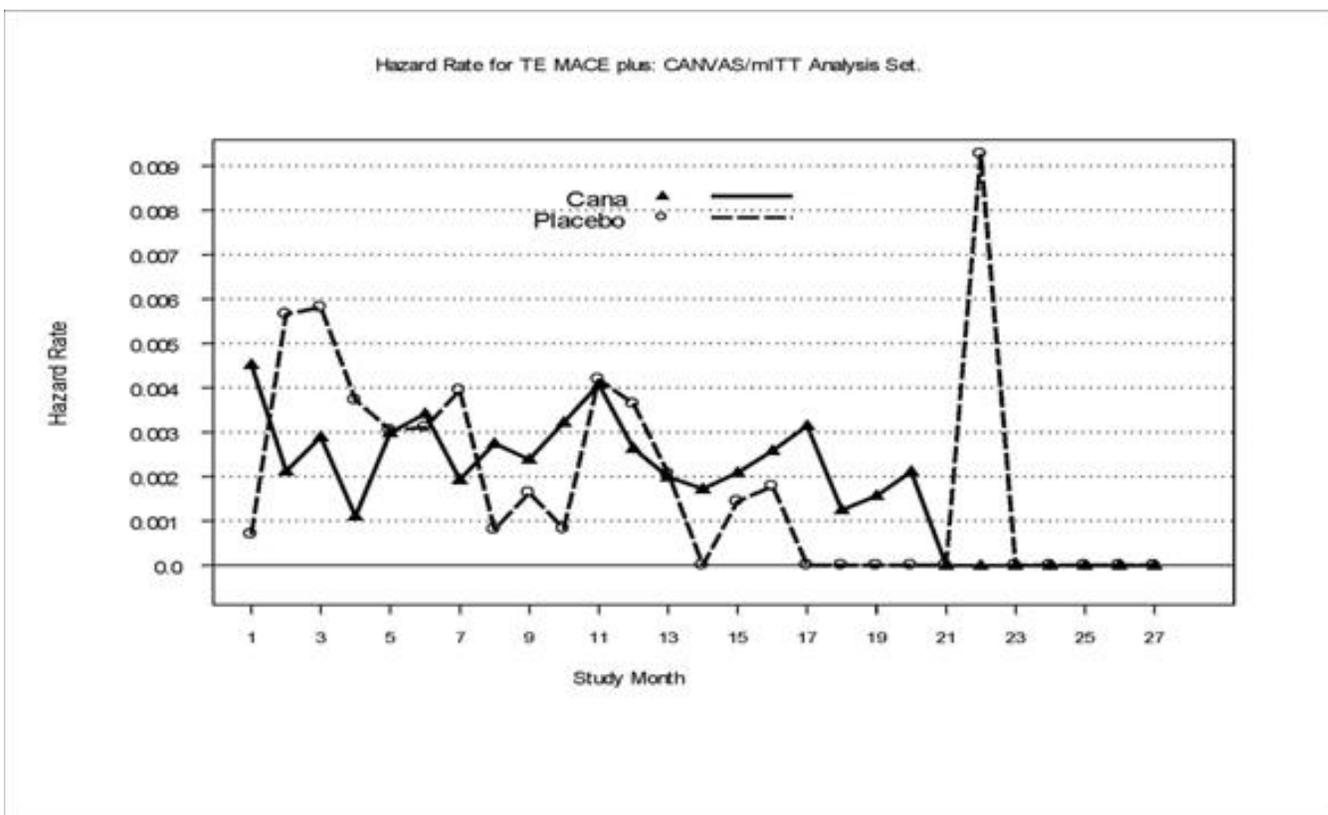
“When both intracranial vertebral arteries are compromised, the most frequent clinical pattern is spells of decreased vision and ataxia, often precipitated by standing or a reduction in blood pressure. In the NEMC-PCR, 13 of 407 patients had hemodynamically sensitive ischemia, most commonly caused by bilateral intracranial vertebral-artery occlusive disease, and they had multiple brief episodes of dizziness, veering, perioral paresthesias, and diplopia.”

Finally, I considered hyperviscosity caused by volume contraction as a triggering event and looked to hemoglobin as a marker. Hemoglobin values for each case were within sex specific normal range at baseline (see table 12 above). No hemoglobin value was available in the narratives during the event. Changes distal to the events > Day 60 were variable and consistent with changes in the overall safety population.

⁶ Savitz S and Caplan L. Vertebrobasilar Disease. New England Journal of Medicine. 2005; 352:2618-26.

The applicant in response to an information request (eCTD sequence11/28/2012) suggested that the early CV imbalance seen in CANVAS was due to the play of chance and makes the following argument to support this assertion;

- No imbalance in early events in the pre-specified meta-analysis was observed
 - 5 vs. 7 vs. 8 MACE+ events in the first 30 days for comparators vs. 100 mg vs. 300 mg
- In CANVAS there was marked month to month variability in occurrence of MACE+ events as is illustrated in the figure showing hazard by month for the two groups.



- Not consistent with timing of volume related events since incidence of volume related events continues to rise steeply up to Day 60 to 90 days
- Not consistent with volume related events because early MACE+ events were not dose related but volume related adverse events are dose-related
- Lack of evidence from large trials (i.e., ALLHAT) that diuretic agents precipitate CV events

Dr. Andraca-Carrera performed several sensitivity analyses to evaluate the robustness of the statistical findings for MACE+ in the first 30 days of CANVAS. He first calculated the predicted number of MACE+ events in the placebo group between Day 0 and 30 given the placebo MACE+ event rate observed in the entire trial. Based on the event rate observed for the entire trial, 3.76 MACE+ events would have

been predicted between Day 0 and 30 on placebo. This lends credence to the theory that a low rate of events in the placebo group may have exacerbated the imbalance in the first 30 days. Dr. Andraca-Carrera then evaluated the stability of the MACE+ hazard ratio estimate in CANVAS for the first 30 Days of the trial. He demonstrates that the hazard ratio in the first 30 Days was unstable and sensitive to the addition of a few additional events in the placebo group. This is shown in table 17 of his review copied below.

Table 17. Sensitivity of the estimated hazard ratio to additional MACE-plus during the first 30 days of CANVAS

	Canagliflozin N = 2886	Placebo N= 1441	Hazard Ratio
Observed data	13	1	6.49 (0.85, 49.64)
1 additional event on placebo	13	2	3.25 (0.73, 14.38)
2 additional events on placebo	13	3	2.16 (0.62, 7.59)
3 additional events on placebo	13	4	1.62 (0.53, 4.97)

Source: Created by reviewer. Dataset: adttecv.xpt

Increases in LDL Cholesterol

This topic has been reviewed in details by Dr. Kwon. Canagliflozin use was associated with a dose dependent increase in LDL cholesterol. The comparator subtracted LS mean change from baseline to the primary efficacy time point across all Phase 3 trials ranged from -2.0 to +8.5% for the canagliflozin 100 mg dose and from +2.8 to +12% for the canagliflozin 300 mg dose. The changes were seen as early as 18 weeks and persisted unchanged at Week-52. Changes observed for calculated measures were consistent with direct measures of LDL in Trial DIA3005 and DIA3006. Initiation of statin therapy in the core trial period of DS-1 was similar between groups (i.e., 1.9%, 2.0 and 1.6% for the placebo, 100 and 300 mg dose). Review of statin initiator data in the dedicated CVOT trial did not suggest differential statin use between arms. The applicant measured Apo B concentration in two trials (DIA3005 and 3006) and assessed LDL particle size using nuclear magnetic resonance spectroscopy in DIA3006 only. These evaluations revealed that the LDL cholesterol increases were accompanied by a rise in Apo B particle numbers and an increase in the amount of large LDL particles.

Other Lipid Parameters

Across the DS-1 trials use of canagliflozin trended toward increasing HDL-cholesterol (~4-5%) relative to placebo. Across these same trials use of canagliflozin was associated with a smaller rise in serum triglycerides relative to placebo between baseline to end-of-treatment. Refer to Dr. Kwon's review for details.

Reviewer Comment:

The imbalance in early MACE+ events in a population at high risk for CV event is concerning however these data have very important limitations and the argument that the imbalance occurred due to ‘play of chance’ can not be refuted.

First, these data were derived from post-hoc, subgroup analyses. Indeed, these data are based on a very restricted time window within a single trial in a group of nine trials included in a pre-specified meta-analysis. These data are not consistent with the overall CV safety data. The overall cardiovascular risk assessment, whether based on MACE+ or MACE, is robust in that it was pre-specified and carried out in a high risk population and is not suggestive of excess risk. The overall cardiovascular safety data in this NDA, in contrast to another program (i.e., dapagliflozin), is derived mostly (i.e., in terms of exposure and patient numbers) from the dedicated cardiovascular trial enrolling a group of individuals at high risk for CV disease and I expect the estimate derived from the overall population to reasonably reflect patients with diabetes highly susceptible to developing cardiovascular disease.

Second, the hazard ratio estimate from the first 30 days of CANVAS is not stable and changes with the addition of very few events. It is possible that the magnitude of the risk could have been made artificially worse by an imbalance in the number of patients randomized to the canagliflozin group with unstable disease (as illustrated by at least two cases who had signs and symptoms of unstable disease before being randomized to canagliflozin) or by the fact that the actual Day 0-30 MACE+ incidence rate in the placebo-group was below the predicted Day 0-30 MACE+ incidence rate.

The topic of cardiovascular safety including the stroke point estimate, the early imbalance in CV events and the LDL increases was discussed during a one day public advisory committee meeting which took place on January 10th 2013. The prevailing opinion among panel members which included experts in statistics and cardiology was that both early events and the unfavorable stroke point estimates were most likely the result of chance. Some members voiced concerns over the long term impact of the LDL increase. The panel members were asked to vote whether they had (yes vote) or did not have (no vote) residual cardiovascular CV safety concerns based on the interim CV safety analysis data presented to satisfy the recommendations in the Guidance for Industry titled “Diabetes Mellitus – Evaluating CV Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes.” Eight versus seven members had residual concerns but most did not feel that these concerns rose to a level of requiring additional pre-marketing studies. In the following question, the members voted 10 to 5 to recommend approval of canagliflozin. The members recommended requiring post marketing trial(s) to resolve the signals.

I agree with the majority opinion at the AC. I weighed the CV risk signals identified against the total cardiovascular safety data available and the potential benefit of the drug. The overall assessment of cardiovascular safety does not suggest canagliflozin is associated with excess risk. Again, I believe the overall cardiovascular outcomes data to be based on relatively robust and reliable data. The added CV risk associated with an LDL rise has to be weighed against the potential cardiovascular benefit

resulting from weight loss, blood pressure reduction, rise in HDL-cholesterol and improved glycemic control unique to this drug class.

However, in light of the early event imbalance, the temporal association with drug initiation and the plausibility that at least some CV events could have been triggered by volume related issues (i.e., blood pressure changes and/or hyperviscosity), I recommend we continue to follow the signal of early CV-events in the dedicated cardiovascular outcomes trial which will be required post-marketing. To mitigate the risk of volume related issues, I recommend: limiting the use to subjects with an eGFR above 45 mL/min/m², warning prescribers of the potential for hypotension, suggesting mitigation strategies to minimize the risk and describing in details characteristics of subjects at most risk for developing hypotension. To resolve the imbalance in stroke events noted in the data submitted with the NDA and the impact of LDL increase, I recommend the applicant performs the definitive cardiovascular safety assessment (i.e., ruling out 30% excess risk) based on MACE only in a population of patients at high risk of cardiovascular disease (i.e., Similar to CANVAS).

Skeletal Safety

This topic has been reviewed in details by Drs. Voss and Kwon. Please refer to their respective reviews for full details.

Two issues of potential relevance to bone safety were identified in the canagliflozin program. As a result of findings related to mineral and bone metabolism in the nonclinical toxicology studies (see nonclinical section of this memorandum) the applicant was asked to assess bone and mineral metabolism in Phase 2 and 3 development. Changes to bone and mineral metabolism were observed in the clinical program and are summarized below. In addition, more upper extremity fractures were observed in patients randomized to canagliflozin than in patients on comparator. These issues do not appear to be related and will be considered separately in this memorandum.

Changes to Bone Metabolism in Clinical Studies

In DIA2001, a 12-Week, phase-2, multiple ascending dose study, carried out in relatively healthy patients with type 2 diabetes use of canagliflozin was associated with a 14 to 28% placebo-adjusted rise in serum markers of bone resorption (collagen type 1 beta-carboxy-telopeptide). The rise was not dose-dependent above a 50 mg per day dose, was observed at Week 3 and persisted to Week 12 inclusive. Changes were also noted in hormones involved in mineral and bone metabolism. Serum parathyroid hormone levels increased from baseline and both 25-OH vitamin D and 1,25-OH vitamin D decreased at high doses.

In light of these findings, the applicant is carrying out a dedicated trial (i.e., DIA3010) in adults older than or equal to 55 years old with osteopenia (for women participant

must be at least three years post-menopause). The trial is randomized, double blind and placebo controlled. The trial duration is 104-weeks divided into a 26 week core efficacy phase and a 78 week extension phase. A key objective of this study is to assess bone turnover markers and bone mineral density using various methodologies over time. 714 patients were enrolled and randomized 1:1:1 to placebo, canagliflozin 100 mg and canagliflozin 300 mg.

The changes from baseline to Week 26 and 52 in bone turnover markers and in hormones involved in bone metabolism observed in DIA3010 was available in the NDA and are summarized in the figure below (Source: Slide 46 Dr. Kwon's presentation EMDAC January 10th 2013). The figure shows that canagliflozin causes a statistically significant, dose-dependent, increase in the serum bone resorption marker beta-CTX relative to placebo and variable changes to serum markers of bone formation. Dr. Voss interprets these changes as having the potential to result in changes to bone mineral density. The study also shows that canagliflozin results in a dose-dependent decline in serum estradiol and a slight non-significant elevation in serum PTH.

Placebo-adjusted changes in bone **resorption and bone **formation** markers**

Placebo adjusted LS Mean **percent change** from baseline to Week-26 and Week-52

	26 Weeks		52 Weeks	
	Cana 100	Cana 300	Cana 100	Cana 300
Serum beta-CTX	↑17.1*	↑24.9*	↑10.3*	↑22.0*
Serum P1NP	↓-5.7	↓-6.9		
Serum osteocalcin	↑3.2	↑4.3	↑9.4*	↑10.1*
Serum estradiol	↓-4.4	↓-13.7	↓-14.2	↓-21.0*
Serum PTH	↑7.0	↑2.0	↑6.2	↑1.5

Beta-CTX = Collagen type 1 beta-carboxy-telopeptide

P1NP=Propeptide amino-term type 1 procollagen

*** 95% CI excludes zero**

The significant changes in bone turnover did not have clinically significant repercussion on placebo adjusted bone mineral density as measured by DXA at 52 weeks (Source: Slide 47: Dr. Kwon's January 10th 2013 EMDAC presentation). The applicant believes these changes are attributable to weight loss and provides examples from the literature to support this assertion.

Changes to **bone mineral density** by DXA

Placebo-adjusted LS Mean percent change (95% CI) from Baseline to Week 52

	Cana 100 (N=241)	Cana 300 (N=236)
Lumbar spine	-0.4 (-1.0, 0.3)	-0.7 (-1.4, -0.1) *
Distal forearm	0.5 (-0.1, 1.2)	0.1 (-0.6, 0.7)
Femoral neck	0.1 (-0.6, 0.8)	0.6 (-0.1, 1.4)
Total hip	-0.4 (-1.0, 0.1)	-0.7 (-1.3, -0.2) *

*** 95% CI excludes zero**

Reviewer Comment: I agree that weight loss could explain the observed findings. Body weight is known to be correlated to bone mass. In addition, the dose-dependent decrease in estradiol levels is consistent with a dose-dependent loss of fat mass and subsequent decrease in the aromatization of dihydrotestosterone to estrogen.

The rise in beta-CTX appears to be out of proportion to the slight non-clinically significant rise in PTH and unlikely to be related. The changes to PTH could be due to renal function changes. The rise in serum phosphorus is consistent with this (i.e., a rise in PTH in subject with normal renal function would be expected to cause hypophosphatemia and not hyperphosphatemia see below). I agree that at this time these changes are not clinically meaningful and recommend that the trial continue to its intended endpoint of 104-weeks.

Changes to Mineral Metabolism:

Canagliflozin use was associated with dose dependent increases in serum levels of calcium, phosphorus and magnesium relative to placebo in a pool of patients with normal renal function and mild renal impairment (DS-1). Changes were small and not clinically meaningful in this population. These changes were more marked in the dedicated trial enrolling patients with moderate renal impairment (DIA3004) and more likely to be clinically meaningful (i.e., more individuals with increases above the upper normal range). The changes over time appeared to parallel changes in renal function for all three mineral metabolites and in my opinion these changes most likely reflect reduced urinary excretion caused by decreased glomerular filtration. Central tendency analyses were consistent with predefined limit of change analyses for all three metabolites. The three figures shown at the advisory committee meeting illustrate the mean change for each mineral metabolite over time in DS-1 and DIA3004.

Figure 12: Mean Changes in Serum Calcium

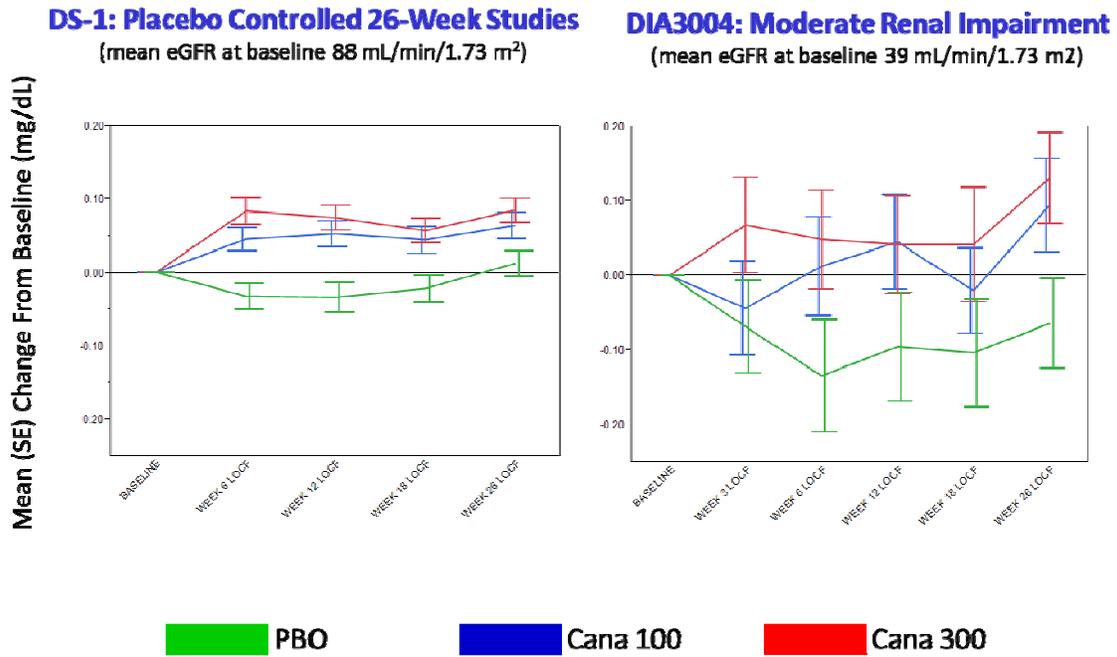


Figure 13: Mean Changes in Serum Magnesium [Mean (SE) Change from Baseline (mg/dL)]

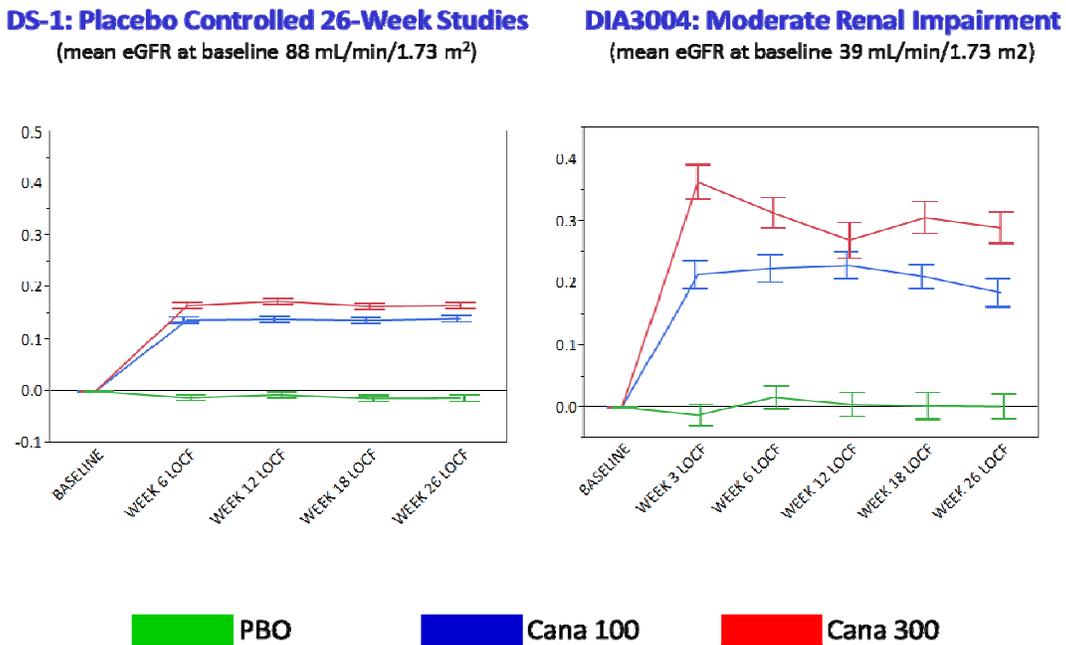
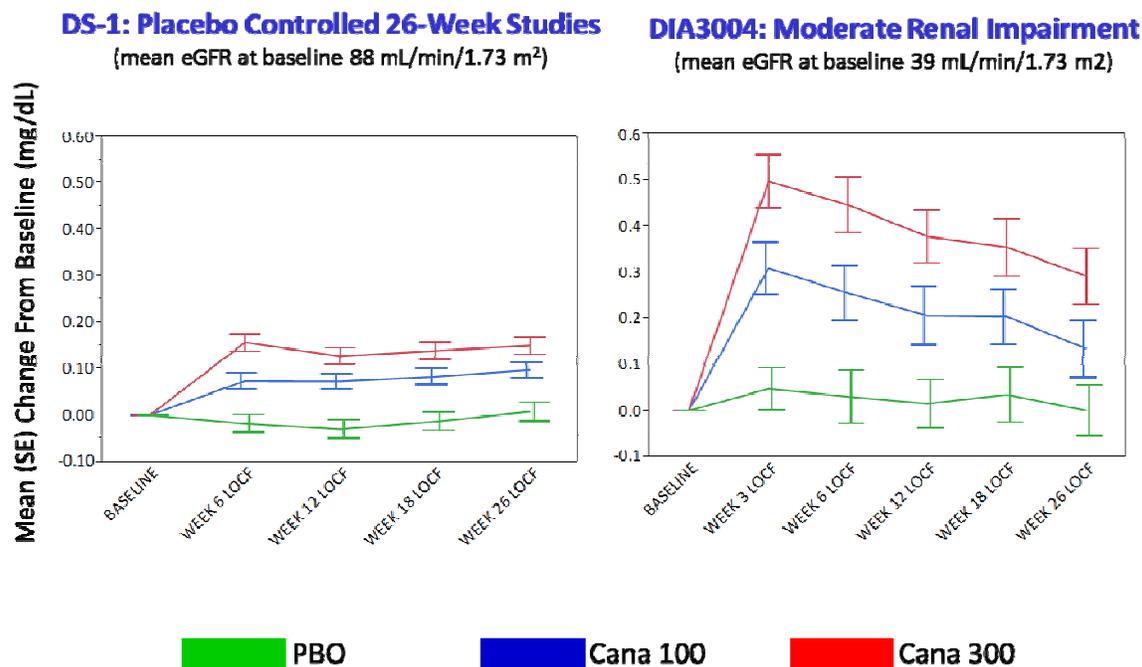


Figure 14: Mean Changes in Serum Phosphorus



Skeletal Fractures:

Higher rates of skeletal fractures were observed in individuals randomized to canagliflozin in DS-4. The fracture imbalance and risk difference did not change appreciably with additional exposure. As of the 4MSU (July 1st 2012), 2.4% versus 1.7% of patients on canagliflozin experienced at least one fracture (18.1 versus 14.2 patients with at least one fracture per 1000 PYE). The imbalance was caused by a greater number of upper limb fractures (i.e., lower limb fractures were slightly lower on canagliflozin). The skeletal locations showing the greatest imbalance were fractures of the humerus, wrist and spine.

Because canagliflozin causes symptomatic hypotension and fractures were mostly located in upper extremities, the applicant reviewed cases of fractures for the concomitant presence of adverse reactions that could suggest hypotension as a precipitating event. One subject was identified (**Case ID# 501524**), this subject had been randomized to canagliflozin 300 mg, had an adverse event of radius fracture and orthostatic hypotension with onset on Day 26.

In DS-3, proportionally more subjects reported at least one adverse event coded to the preferred term “fall” on comparator (0.43%) than on canagliflozin (0.34%). We performed an exploratory analysis of DS-3 using the ADAE.xpt dataset to search verbatim terms for the descriptors “fall, fell and collapse”. This exploratory analysis

revealed that fall events were lost in the process of coding verbatim terms to preferred terms. The table below gives 5 examples of actual verbatim terms identified using this strategy and contrasts these to the preferred term to which these were coded. Using this strategy, we identified 84 cases of falls in contrast to the 35 identified using the preferred term search strategy. In this analysis, subjects randomized to canagliflozin were more likely to experience at least one fall event (0.97%) than subjects on comparator (0.74%). Incident adverse events of hypotension were more commonly reported in patients on canagliflozin (than on comparators) in these 84 cases.

Although a direct link between hypotension, fall events and fractures could not be established with definitive certainty from the available data. The exploratory fall analysis suggests falls occur more frequently on canagliflozin and that the types of fall [i.e., those listed below and others not shown (e.g., “fell on back”)] could result in upper extremity or spine skeletal trauma.

Verbatim Term	Preferred Term
Painful left wrist from fall	Arthralgia
Facial Bruising after fall	Contusion
Patient had a fall, wound on the back of his head.	Head injury
Right shoulder trauma after fall	Joint injury
Swollen left index finger, from fall	Oedema peripheral
Hematoma right hip (after fall)	Haematoma

Reviewer Comment: It is unlikely, given the small magnitude of the observed bone metabolism and bone mineral density changes that these explain the increased fracture incidence. In light of the fracture location, it is possible to speculate that the increase incidence of fractures on canagliflozin were due to falls which could have been provoked by events of hypotension. I recommend we continue to obtain longer term data on bone mineral density by requiring the company to submit the full study report containing 104 week data as a post marketing requirement. I recommend adequately labeling “hypotension” as a risk associated with this product to mitigate risk of fractures potentially associated with this event. I recommend following fracture risk in the dedicated post-marketing cardiovascular outcomes trial as an event of special interest.

At the January 10th 2013 EMDAC advisory committee meeting the panel members were asked to discuss the clinical relevance of the changes related to bone metabolism and density and interpret them in light of the increased fracture incidence. Overall members did not believe changes to bone metabolism and density to be clinically meaningful and were in agreement that such changes could be compatible with weight reduction. They did recommend following the BMD assessment out to

104-weeks in the trial carried out in adults with osteopenia. With regards to fractures Dr. Thomas (a member with expertise in bone biology) suggested following this signal in larger post-marketing studies.

Hypoglycemia

The risk of hypoglycemia associated with canagliflozin was found to be similar in magnitude to the risk associated with other non-insulin secretagogue products. The magnitude to the risk is relatively low. The risk is increased when canagliflozin is co-administered with either insulin or insulin secretagogues as is expected. These data are presented in Dr. Kwon's review.

Reviewer Comment: I recommend labeling the observed findings as they relate to hypoglycemia. The Warning and Precautions section of the label will alert prescribers of the augmented risk in specific clinical use settings highlighted above.

Genitourinary Tract Infection

For a detailed description refer to Dr. Kwon's review.

Glycosuria increases the risk of genital mycotic infection. Since canagliflozin's mechanism of action relies on glycosuria it is not surprising that its use was associated with an increased incidence in adverse reactions related to male and female genital mycotic infections relative to comparator. The adverse reaction was common (> 10% in females; 2-10% in males). The risk increase relative to comparator was 3 to 7-fold higher and was dose not dose dependent. More subjects on canagliflozin had: recurrent events, required anti-fungal therapy or a combination of anti-fungal anti-microbial therapy to treat the infection and had longer mean duration of infection than comparators. In a small number of patients (<<1%) and in particular in male patients, complications of male genital mycotic infections which met the regulatory definition of 'serious' surgical procedures to treat complications (i.e., phimosis) were more common.

Reviewer Comment: It is clear that canagliflozin augments the risk of genital mycotic infection. This infection was not completely anodyne as it did lead to increased minor (drugs) and relatively major (surgery) medical interventions. This adverse reaction and the consequences of such reactions will be clearly delineated in the drug label. It is likely that recurrence of this adverse reaction will result in patients discontinuing treatment with this drug class.

Bladder, Breast, Renal, Testicular and Adrenal Neoplasm:

As of November 15th 2012, there were no imbalances in the number of individuals with bladder or breast or renal or testicular or adrenal neoplasms in the entire safety database. Incidence for renal, bladder, and breast cancers are summarized in Table 91 in Dr. Kwon's review.

Vital Sign and EKG changes

Dr. Kwon has summarized mean changes from baseline in heart rate and blood pressure. Blood pressure changes were discussed in the context of efficacy. Use of canagliflozin was associated with a mean decrease in heart rate of 1 beat per minute in DS-1 based on EKG assessment (See Table 231 in ISS). Changes based on pulse rate assessment during physical exam were smaller than 1 beat per minute. Predefined limit of change analysis did not reveal that more subjects on canagliflozin experienced clinically significant bradycardia in DS-1 (i.e., heart rate below 50 beats per minute). No changes in heart rate were noted in the moderate renal impairment population on EKG. However, slightly more subjects on canagliflozin experienced at least one event of a pulse below 50 beats per minute in the moderately impaired population (5.1%, 8.4%, 7.7% for placebo, canagliflozin 100 mg, and canagliflozin 300 mg (see Table 235 in ISS). We searched the largest integrated safety dataset (ADAE.xpt DS-4) for all adverse events preferred terms which could be related to heart block or bradycardia. Individual events using this search strategy were generally balanced between arms. No clinically significant changes in EKG intervals (including PR) were noted on central or outlier analyses.

Labs:

Changes to clinical laboratory parameter values are discussed above and in Dr. Kwon's review. Mean increases in hematocrit and in hemoglobin levels were seen consistently with use of canagliflozin. The placebo adjusted mean increase in hemoglobin in DIA3008 at Week 52 (mean baseline ~ 14.0 mg/dL for all three groups) in the 100 mg and 300 mg dose groups was 0.77 mg and 0.84 mg/dL, respectively. More subjects on canagliflozin changes exceeding 0.2 mg/dL compared to comparator in DS-1 and DS2. The applicant attributes these changes to hemoconcentration resulting from volume contraction.

• **Advisory Committee Meeting**

An advisory committee meeting was held on January 10th 2013. Discussions at the meeting focused on the cardiovascular, renal and skeletal clinical safety findings in the canagliflozin Phase 3 program. The major cardiovascular and bone safety issues discussed at the advisory committee have been covered in the sections of my memorandum dedicated to these topics. A large part of the committee discussion focused on defining the therapeutic role of canagliflozin in the population of patients with type 2 diabetes who also have moderate renal impairment (~20%⁷ of the 19 million individuals diagnosed with diabetes United States have an eGFR below 60 mL/min/1.73 m²). Members were asked to weigh the findings of glucose lowering in this population and to interpret this benefit in light of the identified risks (hypotension, renal function and electrolyte changes). The two members with expertise in

⁷ Source: United States Renal Data System; 2012 Atlas of CKD and ESRD

nephrology did not feel that any of the renal safety issues presented would preclude use of canagliflozin in a restricted segment of the moderate renal insufficiency population and in particular in subjects with an eGFR above the median value for this category (i.e., eGFR > 45 mL/min/1.73 m²). They did recommend highlighting specific risks which could impact renal function or could be magnified in the renal impaired population through labeling so that prescribers could make an informed decision when contemplating use of canagliflozin in an individual patient. In light of the diminished efficacy and the heightened risks associated with less functional kidney reserve, they did not feel canagliflozin should be used in the general population of patients with an eGFR at the lower end of the moderate renal impairment spectrum.

At the end of the day the committee was asked to vote on the following question:

Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of canagliflozin for the treatment of Type 2 diabetes mellitus?

The results of the vote and summary of the members' rationale derived from the meeting minutes are recopied below:

Yes: 10 No: 5 Abs: 0

Committee Discussion: The committee members who voted "yes" expressed confidence in the efficacy data, as well as the promise of a new mechanism of action which is not dependent on insulin. Some committee members cited strong results on the primary endpoint. One member specifically cited a positive impact for patients, with weight loss and limited hypoglycemia. Those committee members who voted "yes" consistently expressed a remaining desire for further study of cardiovascular effects, especially in longer term exposure. Several members also described a concern over usage in patients with moderate renal impairment, with many mentioning that their support for a favorable benefit-risk profile did not extend to these patients. Those committee members frequently stated that the drug labeling should reflect concerns in these patients. Please see the transcript for details of the committee's discussion.

• **Pediatrics**

The proposed pediatric study plan was reviewed by the pediatric review committee on February 7th 2013. The pediatric review committee was in agreement with the following study plan:

- The pediatric study requirement for ages 0 through 9 years will be waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

- The submission of the pediatric studies for ages 10 to 17 years for this application will be deferred because this product is ready for approval for use in adults and the pediatric study have not been completed.

The deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act will be required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below.

- *A clinical pharmacology study in pediatric patients with type 2 diabetes to evaluate (b) (4) pharmacokinetics, pharmacodynamics, and safety of canagliflozin in older children and adolescent subjects 10 to <18 years of age with type 2 diabetes on metformin monotherapy. This study will include (b) (4)*

Dates for: Final Protocol Submission, Study/Trial Completion, Final Report Submission are being negotiated at this time. The timeline for this PK/PD study will be in keeping with precedent applications for type 2 diabetes.

- *A 26-week, randomized double-blind, placebo-controlled trial, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus, as add-on to metformin (b) (4)*

Dates for: Final Protocol Submission, Study/Trial Completion, Final Report Submission are being negotiated at this time. The timeline for this efficacy and safety study will be in keeping with precedent applications for type 2 diabetes and strive toward ensuring a timely assessment of the efficacy and safety of canagliflozin in children.

- **Other Relevant Regulatory Issues**

None identified. Please refer to the memorandum from the office of scientific investigation for details.

- **Labeling**

A major labeling issue which I will cover in this memorandum relates to dosage and administration. The applicant had proposed recommending the use of canagliflozin 100 mg and 300 mg once daily before the first meal of the day for all patients with an eGFR of ≥ 30 mL/min/1.73 m² and limiting the use of canagliflozin in patients with an eGFR below 30 mL/min/1.73 m². The applicant had also recommended considering a starting dose of 100 mg per day in elderly patients, patients on loop diuretic and patients with an eGFR in the moderate renal impairment range.

We did not agree that the data in the NDA supported such dosing recommendations. We recommend that the drug be contraindicated in patients with severe renal impairment, end stage renal disease and on dialysis. In light of the drug's glucose lowering mechanism of action, there is no prospect of benefit in this population. We recommend against use of the drug in patients with an eGFR below 45 mL/min/1.73 m². Glycemic lowering benefit at the 100 mg dose was minimal and risks associated with volume contraction, renal function impairment and electrolyte disturbances were magnified in this population. Although the 300 mg dose was associated with slightly greater glucose reduction the risks of all the aforementioned changes were further augmented at this dose.

Prescribers will be told to assess renal function before prescribing canagliflozin. This was felt to be reasonable since renal function along with proteinuria is routinely checked in patients with diabetes to monitor for the presence and progression of diabetic nephropathy.

In patients with an eGFR between 45 and 60 mL/min/1.73 m², we recommend the dose be limited to 100 mg per day. In this subpopulation of patients and at this dose the glycemic lowering benefit was judged to be clinically meaningful. Subjects with an eGFR above this level have more functional kidney reserve than subjects in the lower half of the moderate renal impairment range and are expected to be less susceptible to the volume related risks highlighted in the paragraph above. The office of clinical pharmacology had suggested allowing titration up to the 300 mg dose in this subpopulation for patients tolerant of the 100 mg dose. While this was a reasonable approach, the clinical review team did not agree with this dosage recommendation on the basis that the incremental glucose lowering benefit gained by using the higher dose was minimal, unlikely to be clinically meaningful and associated with an augmented risk of adverse reactions related to volume contraction.

To minimize the risk of volume related reactions in future users of canagliflozin, the medical and clinical pharmacology reviewers recommend initiating canagliflozin at a dose of 100 mg once daily per day and reserving the dose of 300 mg per day for patients with an eGFR ≥ 60 mL/min/1.73 m² who are at low risk of hypovolemic complications and require additional glucose lowering. A titration approach was judged as a sensible approach to minimize volume related risks since the major identified risks were dose-dependent. This approach also simplifies the dosing

recommendations and is expected to minimize the potential for dosing errors compared to dosing recommendations that use different starting doses for different segment of the population.

Extensive changes were made to the **Warnings and Precautions** section of the label. This section was changed to: prominently feature volume contraction-related serious adverse reactions which occurred on canagliflozin in the clinical program (e.g., hypotension, renal function impairment, electrolyte changes), identify groups of individuals susceptible to developing those complications and propose monitoring strategies to avoid occurrence of these complications when contemplating the use of canagliflozin to treat diabetes.

A medication guide was recommended by the DRISK evaluator (Dr. Vega). The basis for requiring the medication guide will be to highlight the risk, sign and symptoms of genitourinary infection and adverse reactions related to volume contraction.

- **Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

I recommend Approval pending agreement on final labeling.

- Risk Benefit Assessment

The data in the NDA support an overall conclusion that use of canagliflozin in patients with type-2 diabetes who have an eGFR ≥ 45 mL/min/1.73 m² offers benefits that are not outweighed by the risk associated with use of the drug.

Benefit

Canagliflozin provides clinically meaningful reductions in glycemia in the monotherapy, add-on to single agent therapy and add-on to dual agent therapy setting. In the add-on therapy setting, the 300 mg canagliflozin dose trended towards offering significantly greater glucose lowering than a sulfonylurea (DIA3009) or a DPP-4 inhibitor (DIA3015) at trial end (Week 52 LOCF). The magnitude of the glycemic reduction seen for both doses of canagliflozin is larger than the glucose lowering expected of other currently approved products (e.g., acarbose, pramlintide, colesevalam and bromocriptine). Canagliflozin offers some potential benefits that are not currently offered by approved anti-diabetic products. In contrast to insulin and insulin secretagogues canagliflozin poses a relatively small risk of hypoglycemia. In contrast to insulin, insulin secretagogues, and thiazolidinediones canagliflozin causes less weight gain and in some studies causes a moderate amount of weight loss. In contrast to all currently approved anti-diabetics, canagliflozin use results in significant reductions in blood pressure.

Risks

Several risks associated with the use of canagliflozin were identified in the program. A clear causal relationship was established for the risk of genital mycotic infections the risk associated with adverse reactions related to volume contraction (e.g., hypotension, impairment in renal function and changes to electrolyte handling) and the risk of hypersensitivity reactions. In my opinion, the imbalance in upper extremity fractures is also indirectly related to volume contraction through hypotension (see *Skeletal Safety* section for details) and would be expected to be reduced with mitigation strategies aimed at reducing hypotension. The aforementioned risks, other than fractures, did not, for the most part, result in serious clinical outcomes.

The risk of genital mycotic infection associated with canagliflozin use will be featured prominently on the label. I would expect that a patient who experiences a recurrent or a serious complication from a genital mycotic infections and who is aware that it may be caused by canagliflozin will not want to continue using the product.

The risks associated with volume contraction can be mitigated through labeling. This risk was found to be higher in patients with the following baseline characteristics: low eGFR, advanced age and use of certain concomitant therapies. It is likely that these baseline variables are not independent (i.e., elderly patients are more likely to have low eGFR and be on multiple medications) and our dosage recommendations which limits the use of canagliflozin to patients with a baseline eGFR of ≥ 45 mL/min/1.73 m² may also reduce the risk in elderly and patients with poly-pharmacy. To further reduce the risk, the **Warnings and Precautions** section of the label will: warn prescribers of these risks; highlight characteristics of patients at most risk; and recommend prospective monitoring strategies to avoid the occurrence of these reactions (e.g., consider volume status, renal function, electrolyte assessment prior to initiating canagliflozin). These reactions are commonly observed for therapies used to treat blood pressure (e.g., diuretics, renin and angiotensin blocking agents) and prescribers will be familiar with the recommendations to minimize the risk. Since these are novel adverse reactions for anti-diabetic agents they should be featured prominently on the label.

The risk of hypersensitivity reactions will be labeled and subjects will be recommended to discontinue therapy in the event these reactions occur. Enhanced pharmacovigilance for serious hypersensitivity reactions will be required post-marketing.

There are residual areas of uncertainty for specific potential risks. My opinion related to the risk related to cardiovascular safety of canagliflozin can be found under the “*reviewer comment*” which follows the section of this memorandum labeled *Cardiovascular Safety*. In summary, I believe the interim cardiovascular safety analysis is sufficiently reassuring to allow marketing of canagliflozin. The sponsor will be required to exclude a 30% increase risk relative to placebo using the most robust data post-approval (e.g., data derived from a double blind placebo controlled

cardiovascular outcomes trial using MACE as the primary endpoint). We will require timely fulfillment of this requirement under FDAAA.

The impact of bone metabolism changes on bone mineral density and fractures will be followed in the ongoing trial in older adults with osteopenia.

Another theoretical risk relates to the observation of renal cell carcinoma, pheochromocytoma and leydig cell tumors in the rat carcinogenicity study. No imbalances were seen in the program. It is not feasible to power clinical development program to exclude these risks. The applicant was asked to set-up an enhanced pharmacovigilance plan to follow these potential risks for 10 years following drug approval.

Risks related to pregnancy and lactation will be labeled.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management will be required.

- Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing studies will be required under FDCA 505(o)3.

At the time of this review the dates and final language for some of the postmarketing required studies are under discussion.

- *An assessment and analysis of all foreign and domestic spontaneous reports of malignancy (pheochromocytoma, Leydig cell tumor, and renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy in patients treated with canagliflozin. The enhanced pharmacovigilance should continue for 10 years from the date of approval for malignancies and 5 years for all other events.*
- *Completion and submission of the final study report for the 78-week double-blind extension phase of study DIA3010, to assess the long-term safety of canagliflozin, including, but not limited to, the effect of the addition of canagliflozin to the addition of placebo on bone mineral density and markers of bone turnover.*
- *A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE – non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) in patients with type 2 diabetes mellitus. The primary objective of the*

trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE observed with canagliflozin to that observed in the comparator group is less than 1.3.

The two pediatric studies required under PREA have been discussed above.

- Recommended Comments to Applicant

None.

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/s/

JEAN-MARC P GUETTIER
03/25/2013

MARY H PARKS
03/25/2013